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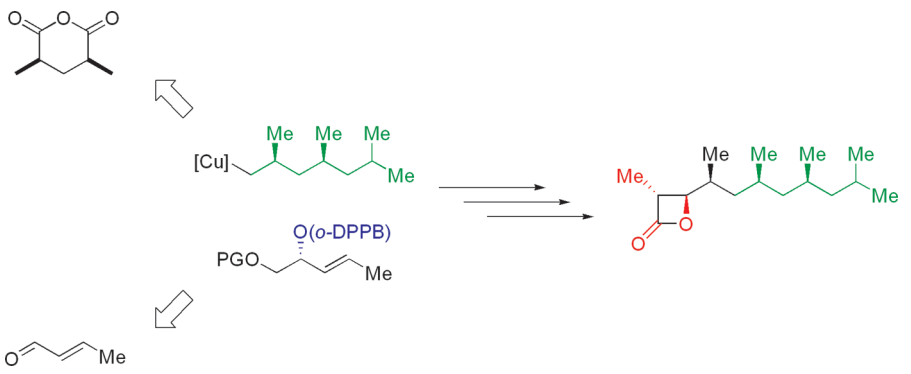
Enantioselective Total Synthesis of the Unnatural and the Natural Stereoisomers of Vittatalactone

Yvonne Schmidt, Konrad Lehr, Ulrich Breuninger, Gabriel Brand, Tomislav Reiss, and Bernhard Breit*

Institut für Organische Chemie und Biochemie, Freiburg Institute for Advanced Studies (FRIAS), Albert-Ludwigs-Universität Freiburg, Alberstr. 21, 79104 Freiburg, Germany

bernhard.breit@chemie.uni-freiburg.de

Received March 4, 2010



The striped cucumber beetle, *Acalymma vittatum*, is a cause of major damage to cucurbit crops in North America. To develop an environmentally benign plant protection strategy, recent research has focused on identifying sex pheromones of the cucumber beetle. In this context, we developed the asymmetric total synthesis of the aggregation pheromone of *A. vittatum*, Vittatalactone, to determine its absolute configuration and to further examine the pheromone response in field studies. The synthesis features an enzyme-catalyzed approach toward the deoxypropionate structural motif. A preformed organocopper reagent could then be coupled in an enantioselective *o*-DPPB-directed allylic substitution with a functionalized *o*-DPPB-ester. By means of this efficient transformation, Vittatalactone could be obtained following a highly convergent synthetic process.

Introduction

Vegetable crops are an important commodity in the United States. The Northeastern states, in particular, have a high proportion of their vegetable crop industry invested in cucurbit crops, including squash, melons, cucumbers, and pumpkins.[1] The main insect pest of these cucurbit crops is the striped cucumber beetle, *Acalymma vittatum*, which also serves as the vector for *Erwinia tracheiphila*, a bacterium that causes a lethal wilt disease in cucurbits.[2] On this background, the demand for sustainable plant protection is high, since classical use of insecticides can be extremely expensive and additionally impacts pollinators and natural enemies.

It has been found by Smyth and Hoffmann that feeding by "male pioneers" results in a pheromone signal produced by the males, which attracts conspecifics.[3] This aggregation behavior or concentrated feeding is a key component for the development of a bacterial wilt epidemic.[4] The composition of the pheromone mixture secreted by the feeding male beetles was first analyzed by Morris and Francke, who discovered the main component to be

(1) Cavanagh, A.; Hazzard, R.; Adler, L. S.; Boucher, J. *J. Econ. Entomol.* **2009**, *102*, 1101–1107.

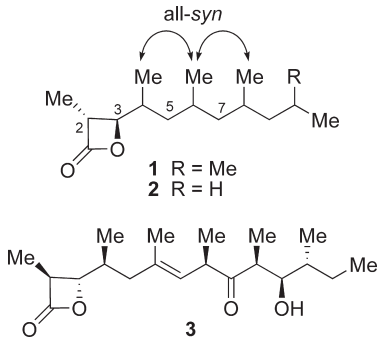
(2) (a) Garcia-Salazar, C. G.; Gildow, F. E.; Fleischer, S. J.; Cox-Foster, D.; Lukezic, F. L. *Environ. Entomol.* **2000**, *29*, 542–550. (b) Garcia-Salazar, C. G.; Gildow, F. E.; Fleischer, S. J.; Cox-Foster, D.; Lukezic, F. L. *Can. Entomol.* **2000**, *132*, 1–13.

(3) (a) Smyth, R.; Hoffmann, M. P. *Physiol. Entomol.* **2002**, *27*, 325–242. (b) Smyth, R.; Hoffmann, M. P. *J. Insect Behav.* **2003**, *16*, 347–359.

(4) (a) Brust, G. E. *Environ. Entomol.* **1997**, *26*, 580–584. (b) Fleischer, S. J.; deMackiewicz, D.; Gildow, F. E.; Lukezic, F. L. *Environ. Entomol.* **1999**, *28*, 470–476.

Published on Web 06/09/2010 DOI: 10.1021/jo100383u

CHART 1. Structures of Vittatalactone (1), 10-Norvittatalactone (2), and Ebelactone A (3)



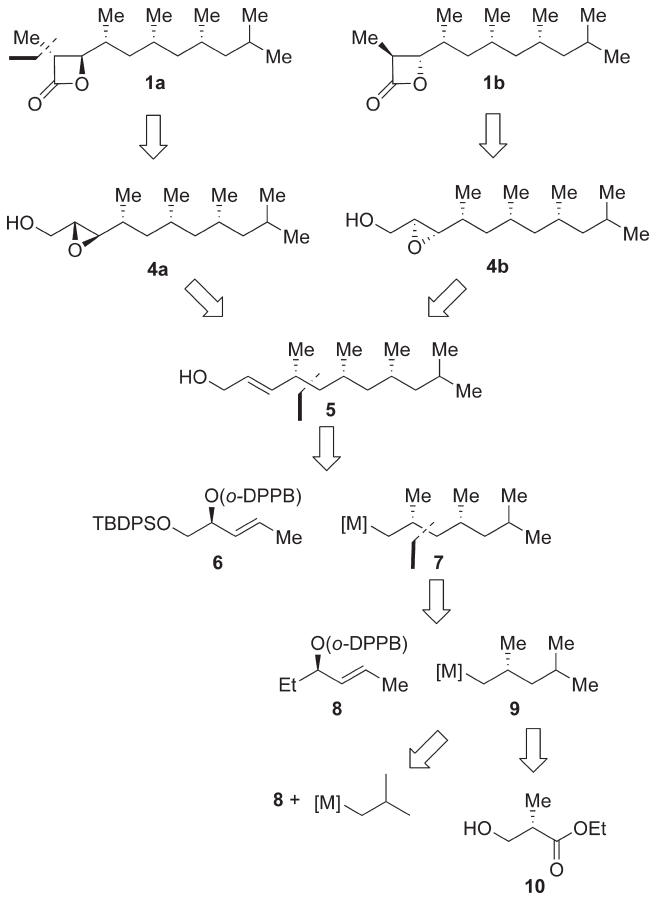
Vittatalactone (**1**), accompanied by a minor compound, 10-Norvittatalactone (**2**).[5] With 5 stereogenic centers, both β-lactones represent very complex structures among physiologically active insect volatiles.

Recently, we reported on the total synthesis of the enantiomer of Vittatalactone based on an iterative allylic substitution concept.[6] By means of the enantiomer synthesis, we were able to elucidate the absolute configuration of the natural product. We herein describe in full detail the evolution of our total synthesis, the determination of the absolute configuration of Vittatalactone through total synthesis of two eventual diastereomers, and finally a new and more convergent as well as scalable synthesis of the natural enantiomer of Vittatalactone (**1**).

Target Structure Assignment. The structure published by the Francke group did not include the stereogenic information on the methyl branched side chain (Chart 1). By NMR analysis of the Mosher ester derivative of the corresponding hydroxy acid, they assigned the stereocenters at C2 and C3 of (**1**) to be (2*R*,3*R*).[5] Unknown at this point was the relative configuration of the alcohol at C3 and the methyl group on C4, while Morris and Francke referred to the close structural relationship of **1** to Ebelactone A (**3**), isolated from a strain of *Streptomyces*, which is an inhibitor of esterases, lipases, and *N*-formylmethionine aminopeptidases.[7] This lactone exhibits an *anti*-relationship between C3 and C4 and results from polyketide biosynthesis, involving propionate-derived subunits, which also seems likely for Vittatalactone (**1**).[8]

In addition to the findings of Morris and Francke, we compared the NMR shifts of the methylene protons at C5 and C7 with the NMR data obtained for other deoxypropionate derived compounds, and this examination resulted in the presumption of an all-*syn* configuration referring to the methyl groups.[6,9] On this background, we chose the *syn*- and *anti*-lactones **1a** and **1b** (Scheme 1), respectively, as our target structures. This is a promising choice, since it would enable us to derive both possible diastereomers of the natural product from an enantioselective Sharpless epoxidation of a common intermediate, allylic alcohol **5**. Hence, such a divergent approach would then allow us to determine the absolute configuration of Vittatalactone.

SCHEME 1. Synthesis Plan for Diastereomeric β-Lactones 1a and 1b



Results and Discussion

First Generation Retrosynthetic Approach. The lactones **1a** and **1b** would be accessible from the epoxides **4a** and **4b**, respectively, by regioselective ring opening with a methyl copper reagent (Scheme 1). We then targeted the allylic alcohol **5** as the common intermediate for the epoxide synthesis. This polyketide structure could be assembled via the iterative *o*-diphenylphosphinobenzoic acid (*o*-DPPB) directed allylic substitution method developed in our group.[10] We have successfully demonstrated this principle in several syntheses,[6,11]

(5) Morris, B. D.; Smyth, R. R.; Foster, S. P.; Hoffmann, M. P.; Roelofs, W. L.; Franke, S.; Francke, W. *J. Nat. Prod.* **2005**, *68*, 26–30.

(6) Schmidt, Y.; Breit, B. *Org. Lett.* **2009**, *11*, 4767–4769.

(7) (a) Umezawa, H.; Aoyagi, T.; Uotani, K.; Hamada, M.; Takeuchi, T.; Takahashi, S. *J. Antibiot.* **1980**, *33*, 1594–1596. (b) Uotani, K.; Naganawa, H.; Kondo, S.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1982**, *35*, 1495–1499. (c) Nonaka, Y.; Ohtaki, H.; Ohtsuka, E.; Kocha, T.; Fukuda, T.; Takeuchi, T.; Aoyagi, T. *J. Enzyme Inhib.* **1995**, *10*, 57–63.

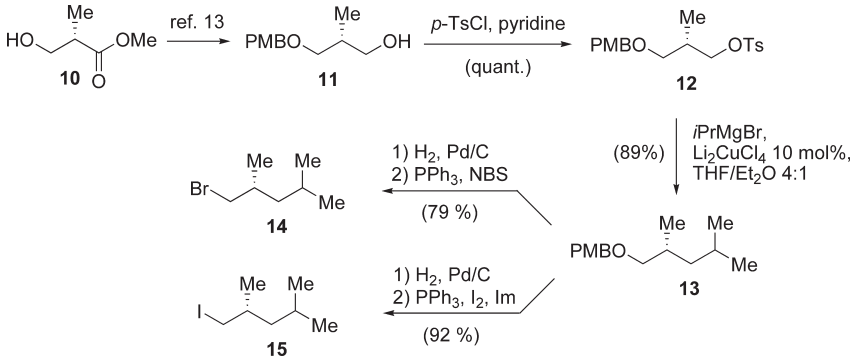
(8) (a) Uotani, K.; Naganawa, H.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1982**, *35*, 1670–1674. For a thorough overview on polyketide biosynthesis, see: Hertweck, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 4699–4716.

(9) By comparison of NMR data we found a strong splitting (0.2 and 0.3 ppm, respectively) for the chemical shift of the methylene protons, which has been shown to be typical for the internal methylene unit of a *syn*-deoxypropionate unit. In case of the *anti*-configured diastereomers the chemical shift differences decrease. For experimental data, see: (a) Herber, C.; Breit, B. *Chem.—Eur. J.* **2006**, *12*, 6684–6691. (b) Herber, C.; Breit, B. *Eur. J. Org. Chem.* **2007**, 3512–3519. (c) Hanessian, S.; Yang, Y.; Giroux, S.; Mascitti, V.; Ma, J.; Raeppel, F. *J. Am. Chem. Soc.* **2003**, *125*, 13784–13792. For a theoretical overview of conformation control, see: (d) Schmidt, Y.; Breit, B. *Org. Lett.* **2010**, *12*, 2218−2221, and references cited therein.

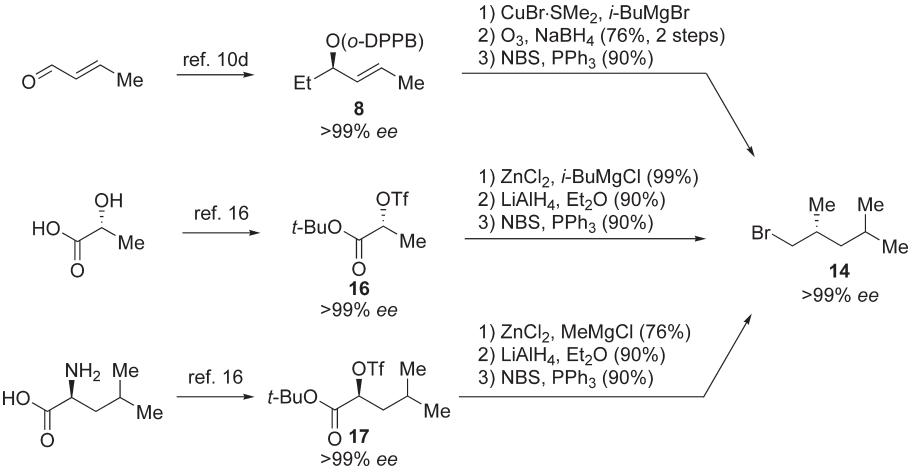
(10) (a) For a recent review, see: Schmidt, Y.; Breit, B. *Chem. Rev.* **2008**, *108*, 2928–2952. (b) Reiss, T.; Breit, B. *Chem.—Eur. J.* **2009**, *15*, 6345–6348. (c) Herber, C.; Breit, B. *Angew. Chem.* **2004**, *116*, 3878−3880; *Angew. Chem., Int. Ed.* **2004**, *43*, 3790−3792. (d) Herber, C.; Breit, B. *Chem.—Eur. J.* **2006**, *12*, 6684–6691.

(11) (a) Reiss, T.; Breit, B. *Org. Lett.* **2009**, *11*, 3286–3289. (b) Rein, C.; Demel, P.; Outten, R. A.; Netscher, T.; Breit, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 8670–8673. (c) Herber, C.; Breit, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5267–5269. (d) Herber, C.; Breit, B. *Eur. J. Org. Chem.* **2007**, 3512–3519.

SCHEME 2. Synthesis of Grignard Precursors 13 and 14



SCHEME 3. Alternative Syntheses of Grignard Precursor 14



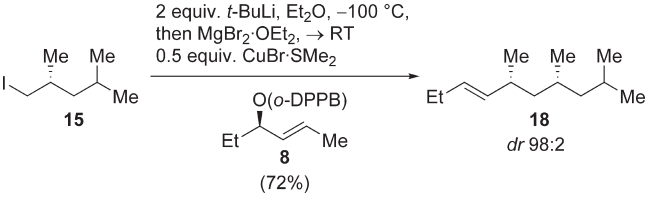
and Vittatalactone provided another challenging test case to explore the generality of this concept. Thus, the common intermediate **5** could stem from a directed allylic substitution of functionalized *o*-DPPB-ester **6** and dideoxypropionyl organometallic reagent **7**. This step could set the third tertiary stereogenic center of the trideoxypropionate unit and would simultaneously introduce the allylic alcohol functionality.

The dideoxypropionyl organometallic reagent **7** in turn could be derived from a second directed allylic substitution employing the deoxypropionate building block **8** and the organometallic reagent **9**. This first tertiary stereogenic center may again be generated on performing an allylic substitution on *o*-DPPB-ester **8** with an isobutyl Grignard reagent. Alternatively, it may stem from the commercially available Roche ester **10**.[12]

Synthesis of (−)-Vittatalactone and Structure Elucidation. Preliminary Study on Allylic Substitution and Synthesis of Dideoxypropionyl Bromide (−)-19. Our synthesis started with monoprotected diol **11**,[13] which is available in two steps from the Roche ester **10** through alcohol protection and hydride reduction of the ester functionality. Alcohol **11** was activated as the tosylate **12** and submitted to the conditions of a copper-catalyzed sp^3-sp^3 cross-coupling reaction with isopropylmagnesium bromide (Scheme 2) to furnish PMB-ether **13** in good yield.[14,15] The preparation of the suitable Grignard precursors, bromide **14** and iodide **15**, was performed as a one-pot procedure because of the high volatility of the intermediate alcohol and the bromide and iodide, respectively.

Additionally, alternative synthetic approaches based on methodology developed in this group toward bromide **14** were studied. Thus, subjection of allylic *o*-DPPB-ester **8** to the conditions of the copper-mediated allylic substitution with isobutyl magnesium bromide furnished the corresponding *syn*-S_N2' product (Scheme 3).[10d] Subsequent ozonolysis followed by a reductive workup and bromination gave bromide **14** in overall good yields. Two alternative syntheses of **14** rely on the zinc-catalyzed enantiospecific sp^3-sp^3 coupling developed recently in our group.[16] Thus, starting from D-lactic acid derived triflate **16**, bromide **14** was accessible in three steps. Notably, the yield in the zinc-catalyzed coupling step with isobutyl

SCHEME 4. First Allylic Substitution Study towards Alkene 15

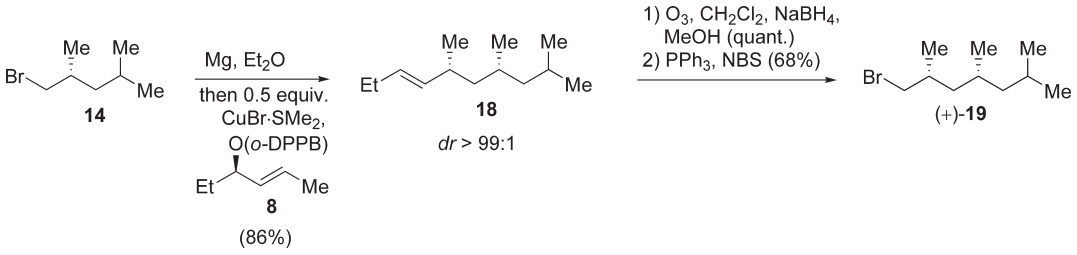


(12) (a) Goodhue, C. T.; Schaeffer, J. R. *Biotechnol. Bioeng.* **1971**, *13*, 203–214. (b) Ohta, H.; Tetsukawa, H.; Noto, N. *J. Org. Chem.* **1982**, *47*, 2400–2404. (c) Molinari, F.; Gandolfi, R.; Villa, R.; Urban, E.; Kiener, A. *Tetrahedron: Asymmetry*. **2003**, *14*, 2041–2043.

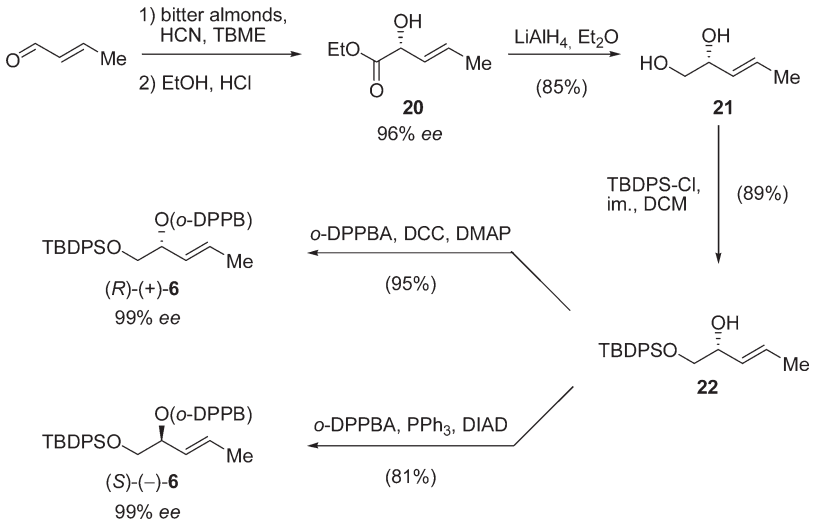
(13) We received the alcohol **10** as a generous gift from Novartis; for synthesis of **10**, see: Walkup, R. D.; Boatman, P. D., Jr.; Kane, R. R.; Cunningham, R. T. *Tetrahedron Lett*. **1991**, *32*, 3937–3940.

(14) Fouquet, C.; Schlosser, M. *Angew. Chem*. **1974**, *86*, 50−51; *Angew. Chem., Int. Ed. Engl*. **1974**, *13*, 82−83.

SCHEME 5. Directed Allylic Substitution and Iteration to Grignard Precursor (−)-19



SCHEME 6. Enantioselective Synthesis of *o*-DPPB-esters (*R*)-(+)-6 and (*S*)-(−)-6



magnesium chloride was essentially quantitative. Alternatively, one may start from triflate **17**, which is readily available through diazotization of L-leucine. Coupling with methyl magnesium chloride, $LiAlH_4$ reduction, and bromination provided a third efficient pathway toward bromide **14**.

Directed allylic substitution using the *o*-DPPB-ester **8**[10c,d] as coupling partner was examined first with the iodide **15**, according to the procedure used in the synthesis of 4,6,8,10,16,18-hexamethyldocosane (Scheme 4).[11c,d] Thus, iodine−lithium exchange was effected upon treatment of iodide **15** in diethyl ether with 2 equiv of *tert*-butyllithium at −100 °C. The thus-obtained organolithium species was transmetalated to magnesium upon warming to room temperature with magnesium dibromide etherate. The resulting Grignard reagent was subjected to the conditions of the directed allylic substitution with 1 equiv of *o*-DPPB-ester **8** to furnish the S_N2' substitution product **18** in good yield and diastereoselectivity.

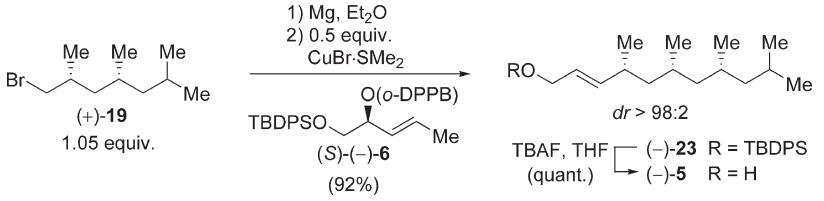
Although this procedure works quite well on a small (1−2 mmol) reaction scale, it has limitations on larger scale. Thus, the use of pyrophoric *tert*-butyllithium in large quantities is undesirable, as is the requirement of the extreme low temperature conditions of −100 °C. To allow for a more convenient and scalable allylic substitution process, we looked at the direct Grignard synthesis starting from bromide **14**. Indeed, the bromide **14** (1.1 equiv) was reduced with magnesium (turnings, etched three times with dibromoethane and thoroughly washed with diethylether) to the corresponding Grignard reagent, which was directly used in the *o*-DPPB-directed allylic substitution with unfunctionalized *o*-DPPB-ester **8** to furnish dideoxypropionate **18** in excellent diastereoselectivity (>99:1) and yield (86% based on the ester, Scheme 5). To incorporate the third propionate unit, we initiated the next iteration, which began with ozonolysis of alkene **18** and a reductive workup to furnish the corresponding alcohol. Mukaiyama redox condensation provided bromide (+)-**19**.[17]

Enantioselective Preparation of *o*-DPPB-esters (*R*)- and (*S*)-6. For installation of the third methyl-branched tertiary stereogenic center with concomitant assembly of the allylic alcohol in **5**, we required access to oxygen-functionalized *o*-DPPB-esters **6**.

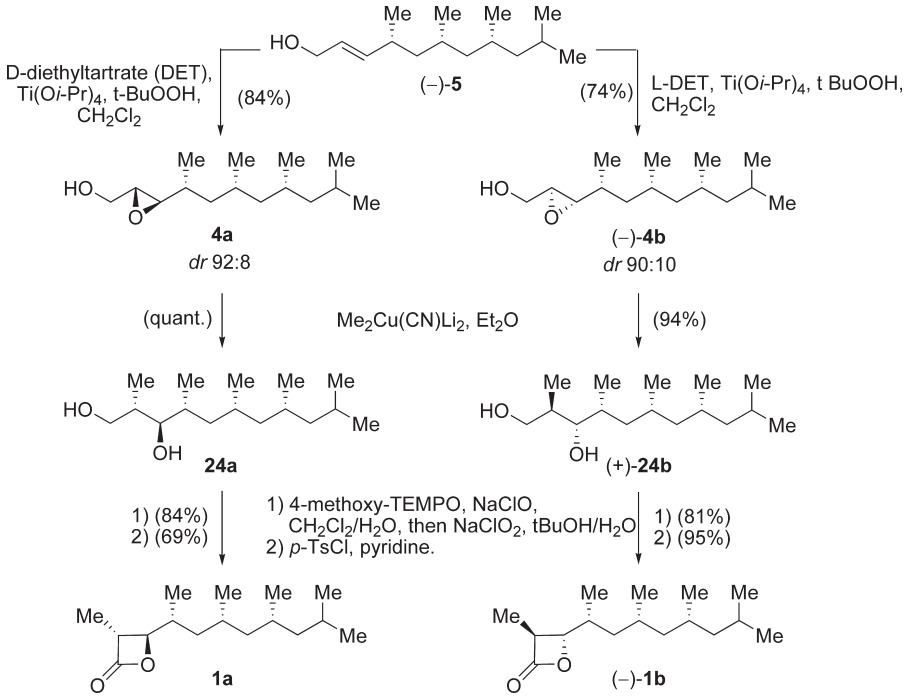
Thus, crotonaldehyde was treated with HCN in the presence of an (*R*)-oxynitrilase readily obtained from grinding and scouring of bitter almonds,[18] which gave the (*R*)-cyanohydrin with high levels of enantioselectivity (>96% ee).[19] Subjecting the cyanohydrin to the conditions of a Pinner reaction furnished the ethyl ester **20** (Scheme 6).[20] The reduction with lithium aluminum hydride led to diol **21**, and subsequent silylation furnished the silylether **22** on a multigram scale.[21] Applying the standard Steglich esterification protocol[22] with *o*-diphenylphosphanylbenzoic

(15) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303–305.
(16) Studte, C.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5451–5455.
(17) Mukaiyama, T. *Angew. Chem.* **1976** *88*, 111−120; *Angew. Chem., Int. Ed.* **1976**, *15*, 94−103.
(18) (a) Rosenthaler, L. *Biochem. Z.* **1908**, *14*, 238–253. (b) Becker, W.; Benthin, U.; Eschenhof, E.; Pfeil, E. *Biochem. Z.* **1963**, *337*, 156–166.
(19) Effenberger, F.; Gaupp, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1765–1775.
(20) Pinner, A.; Klein, F. *Ber. Dtsch. Chem. Ges.* **1878**, *11*, 1475–1487.
(21) Warmerdam, E. G. J. C.; van den Nieuwendijk, A. M. C. H.; Brussee, J.; Kruse, C. G.; van der Gen, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2539–2550.
(22) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem.* **1978***90*, 602−615; *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569−583.

SCHEME 7. ***o*-DPPB-Directed Allylic Substitution towards Allylic Alcohol (−)-5**



SCHEME 8. **Final Steps towards Diastereomeric *β*-Lactones 1a and (−)-1b**



acid (*o*-DPPBA)[23] provided *o*-DPPB-ester (*R*)-(+)-**6** quantitatively. Crystallization of this product improved the enantiopurity to greater than 99% ee. To obtain the requested (*S*)-enantiomer of **6** one could apply a corresponding (*S*)-oxynitrilase. However, such enzymes are far more difficult to access.[24] Hence, we looked at a Mitsunobu inversion protocol, which ideally would use *o*-DPPBA itself as the nucleophile.[25] Since *o*-DPPBA is both a carboxylic acid and a phosphine, we expected this to be a nontrivial reaction because the reagent triphenylphosphine as well as *o*-DPPBA may react with the azodicarboxylate electrophile. Interestingly, we observed a clean Mitsunobu reaction of the allylic alcohol **22** with *o*-DPPBA to furnish the corresponding (*S*)-(−)-enantiomer of *o*-DPPB-ester **6** in good yield (81%). After recrystallization (*S*)-(−)-**6** was obtained in > 99% enantiopurity.

Final Steps toward *β*-Lactones 1a and 1b. With the bromide (+)-**19** and *o*-DPPB-ester (*S*)-(−)-**6** in hand, we could approach the construction of the central allylic alcohol intermediate **5** in our divergent synthesis strategy toward both eventual diastereomers of Vittatalactone. Thus, bromide (+)-**19** was transformed into the corresponding Grignard reagent upon treatment with magnesium in diethylether[26] and, subjected to the conditions of the *o*-DPPB-directed allylic substitution with the oxygen-functionalized *o*-DPPB-ester (*S*)-(−)-**6**, furnished the allyl silyl ether **23** in excellent yield and diastereoselectivity (Scheme 7).[27] Noteworthy, only 1.05 equiv of the valuable bromide (+)-**19** was necessary to achieve full conversion in the directed allylic substitution, which renders this reaction a valuable tool in enantioselective carbon skeleton construction and even suitable for use as a fragment coupling in the course of a convergent total synthesis.[11b] Finally, fluoride-mediated desilylation of **23** liberated the key allylic alcohol (−)-**5** quantitatively.

Transformation of allylic alcohol (−)-**5** toward the two diastereomeric target structures **1a** and **1b** commenced with the catalyst-controlled stereoselective Sharpless epoxidation employing D- and L-diethyltartrate, respectively (Scheme 8).[28] Both diastereomeric epoxy alcohols **4a** and (−)-**4b** were obtained in good yields and diastereoselectivities.

(23) (a) Hoots, J. E.; Rauchfuss, T. B.; Wrobleski, D. A. *Inorg. Synth.* **1982**, *21*, 175–180. (b) Kemme, S. T.; Schmidt, Y.; Grünanger, C. U.; Laungani, A. C.; Breit, B. *Synthesis* **2010**, 1924−1928. (c) o-DPPBA is commercially available on a multigram scale from SinoMax Solutions Co., Ltd., Beijing, China; http://www.sinomaxchem.com.

(24) Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555–1564.

(25) Mitsunobu, O. *Synthesis* **1981**, 1–28.

(26) Careful cleaning of the used Mg powder is essential for this transformation; see also ref 6.

(27) Reiss, T.; Breit, B. *Chem.—Eur. J.* **2009**, *15*, 6345–6348.

(28) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976. (b) For a review, see: Katsuki, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. II, pp 621−677.

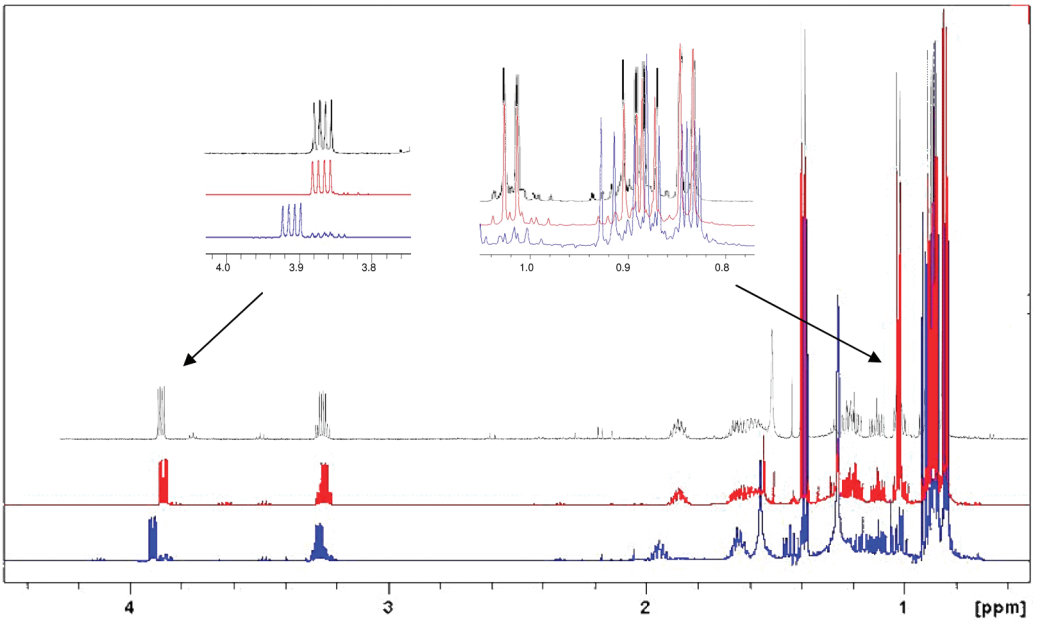
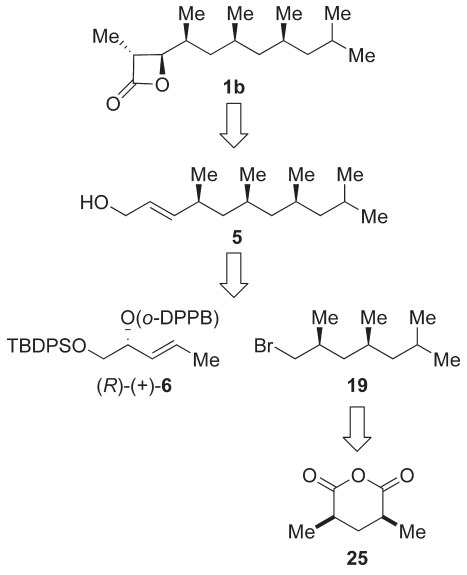
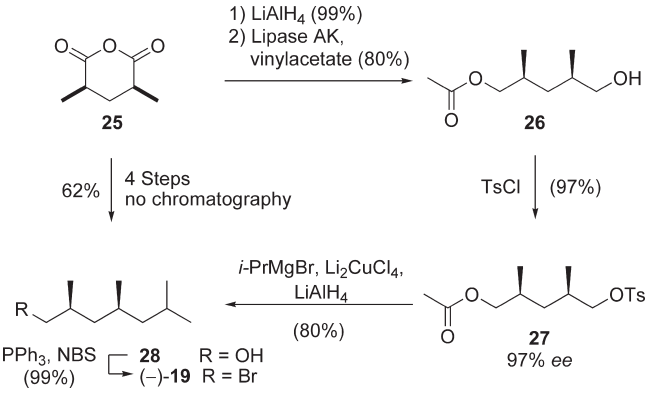


FIGURE 1. Comparison of NMR spectra of natural Vittatalactone (black),[5] β-lactone (−)-**1b** (red), and β-lactone **1a** (blue, dr 92:8).

SCHEME 9. Improved Retrosynthesis of Vittatalactone



SCHEME 10. Alternative Synthesis of Grignard Precursor (−)-19



The carbon skeleton of vittatalactone was completed by addition of cyanodimethylcuprate to give the 1,3-diols **24a** and (+)-**24b**, respectively, in good yield.[29] At this stage, the minor diastereomer of (+)-**24b** (being **24a**) could be separated by column chromatography to provide (+)-**24b** in a diastereomeric ratio of > 98:2. A highly selective oxidation of the primary alcohol of the 1,3-diols **24** toward the corresponding β-hydroxy aldehydes was accomplished applying 4-methoxy-TEMPO/hypochlorite in good yields,[30] even though the proximity of the secondary alcohol renders it a rather difficult synthetic operation.[31] Pinnick oxidation then completed the oxidation step to furnish the respective β-hydroxy acids.[32] The final ring closure was initiated with tosyl chloride in pyridine to give desired β-lactones **1a** and (−)-**1b** in good to high yields.[33]

Structure Elucidation of Vittatalactone. Both diastereomeric lactones **1a** and (−)-**1b** were subjected to NMR spectroscopic analysis. Comparison of the proton and carbon NMR data with those of the natural material isolated by the Francke group showed a complete match for β-lactone (−)-**1b** (Figure 1).[5] Hence, (−)-**1b** possesses the correct relative configuration of the natural product, whereas compared with the Mosher ester structure analysis of Francke et al., β-lactone (−)-**1b** is (2*S*,3*S*)-configured and should therefore be the enantiomer of natural vittatalactone.

Second Generation Synthesis of Natural (+)-Vittatalactone. With the knowledge of the correct absolute configuration of Vittatalactone, we decided to prepare the natural

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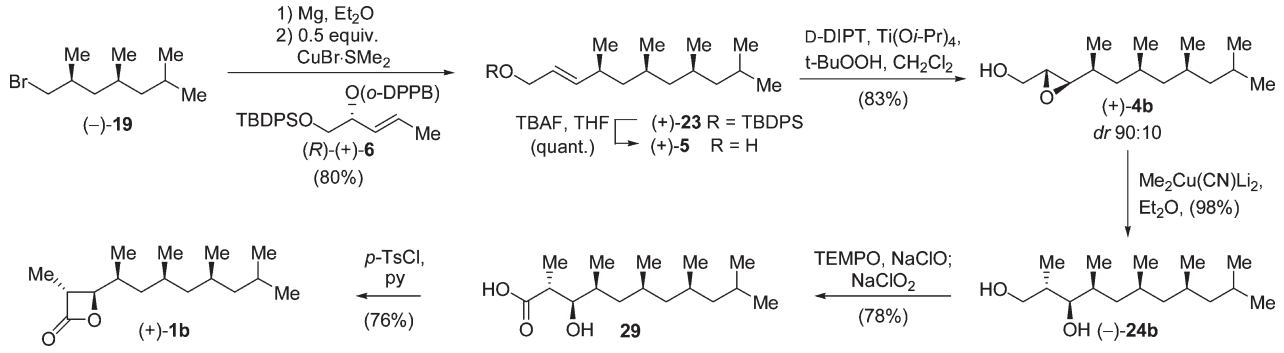
SCHEME 11. Completion of Vittatalactone ((+)-1b) Synthesis



stereoisomer by way of a modified and more convergent synthetic strategy that would allow for the synthesis of enough material for biological studies. Thus, a commercially available starting material for the bromide **19** is the *meso*-anhydride **25** (Scheme 9). Enzymatic desymmetrization of the corresponding *meso*-diol is well-known.[34]

Thus, following the protocol developed by Mori et al., commercially available *meso*-anhydride **25** was reduced with lithium aluminum hydride to the corresponding *meso*-diol (Scheme 10). Subsequent desymmetrization with lipase AK and vinylacetate furnished the monoacetate **26** in high enantiomeric purity (97% ee)[35] in 80% yield. The hydroxy group was activated as a tosylate **27** and subjected to the conditions of a copper-catalyzed sp^3-sp^3 cross-coupling reaction employing an excess of isopropyl magnesium bromide. The resulting alcohol **28** was converted to the bromide (−)-**19** via Mukaiyama redox condensation.[16] Thus, with this route starting from commercially available *meso*-anhydride **24**, the desired dideoxypropionyl bromide (−)-**19** was readily available in large scale in four steps and 62% overall yield employing only one chromatographic purification.

The final steps toward natural Vittatalactone were straightforward according to the enantiomer synthesis (Scheme 11). Allylic substitution with *o*-DPPB-ester (*R*)-(+)-**6** and deprotection afforded the allylic alcohol (+)-**5** with complete diastereoselectivity. We also tried to further enhance the stereoselectivity by using the diisopropyltartrate instead of diethyltartrate at −20 °C.[36] However, the stereoselectivity for the formation of epoxide (+)-**4b** could not be raised beyond a diastereomeric ratio of 90:10.

Subsequently, the oxidation level of Vittatalactone was adjusted employing the selective two-step oxidation protocol developed in the first generation approach, to give the hydroxy acid **29** without any trace of overoxidation to the β-keto acid. Final ring closure to the natural product was accomplished with tosyl chloride in pyridine to furnish natural Vittatalactone ((+)-**1b**) in good yield.

Conclusion

Through total synthesis and comparison of NMR data of synthetic and natural material we could elucidate the absolute configuration of Vittatalactone ((+)-**1b**) from *Acalymma vittatum*. With the development of a more convergent and practical second generation synthesis we could prepare over 50 mg of the natural stereoisomer in 11 steps for the longest linear sequence and a total yield of 18%.

The successful enantioselective synthesis of the two unnatural diastereomers **1a** and (−)-**1b** as well as the natural isomer (+)-**1b** highlights the synthetic power of the directed allylic substitution for deoxypropionate and propionate construction.

Now, the door is open for extensive biological studies to see whether this pheromone can indeed become an environmentally friendly and efficient tool for a cucurbit plant protection strategy in the future.

Experimental Section

(*R*,*E*)-5,7-Dimethyloct-3-ene. (*R*,*E*)-Hex-4-en-3-yl 2-(diphenylphosphino)benzoate (**8**) (402 mg, 1.02 mol, 1.00 equiv, 98% ee) and copper(I) bromide dimethyl sulfide complex (105 mg, 0.510 mmol, 0.500 equiv) were suspended in diethyl ether (20 mL). A solution of isopropyl magnesium bromide in diethyl ether (about 1.0 M, 3.6 mL, 1.2 equiv) was added over 1.5 h at room temperature with a syringe pump. The reaction mixture was stirred for another 1 h until full conversion was observed by TLC. The reaction mixture was directly transferred on a silica gel plug and rinsed with pentane. The resulting solution was washed with aqueous sodium hydroxide (0.25 M, 50 mL) and washed with saturated aqueous sodium hydrogen carbonate (20 mL). Because of the high volatility of the product, it was used in the next step without further concentration or purification. R_f = 0.82 (pentane).

(*R*)-2,4-Dimethylpentan-1-ol. The solution of (*R*,*E*)-5,7-dimethyloct-3-ene in diethyl ether/pentane (about 100 mL) was cooled to −78 °C. Then ozone was bubbled through the solution until a blue color persisted. Immediately afterward nitrogen was purged through the solution until the blue color disappeared. Remaining at −78 °C, sodium borohydrate (1.1 g, 30 mmol, 30 equiv) was added in portions. The reaction mixture was allowed to warm to room temperature overnight. The suspension was quenched with water (30 mL) and stirred vigorously for 2 h. The phases were separated, and the aqueous phase was extracted with diethyl ether (4 × 30 mL). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography (pentane/diethyl ether 1:1, ϕ 2 cm, length 16 cm, fraction size 6 mL, fractions 12−18) to obtain the title compound as a volatile colorless liquid (89 mg, 76% over two steps from **8**). R_f = 0.63 (diethyl ether); $[\alpha]^{24}_D$ = +10.6° (*c* 0.7, $CHCl_3$, 98% ee); to determine the ee the alcohol was converted into the corresponding benzoyl ester ((*R*)-2,4-dimethylpentyl benzoate): HPLC Diacel Chiralpak AD-3 column, heptane/isopropanol 400:1, flow rate = 1.0 mL/min, 20 °C, detection at 227 nm, t_1 = 4.05 min (major), t_2 = 4.72 min (minor).

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The NMR-spectroscopic analysis is consistent with literature data.[7]

(*R*)-2,4-Dimethylpentan-1-ol. Lithium aluminum hydride (33 mg, 0.86 mmol, 2.0 equiv) was suspended in diethyl ether (5 mL) and cooled to −20 °C. Then a solution of (*R*)-tert-butyl 2,4-dimethylpentanoate (80 mg, 0.43 mmol, 1.00 equiv) in diethyl ether (5 mL) was added during 10 min. The reaction mixture was allowed to warm to room temperature overnight. It was cooled back to 0 °C, quenched with saturated aqueous sodium sulfate (0.4 mL), and dried over sodium sulfate. Purification by flash chromatography (pentane/diethyl ether 1:1, ϕ 2 cm, length 16 cm, fraction size 7 mL, fractions 9−15) to obtain the title compound as a colorless liquid (48 mg, 96%). The NMR-spectroscopic analysis is consistent with literature data.[7]

(*R*)-1-Bromo-2,4-dimethylpentane (14). A solution of (*R*)-2,4-dimethylpentan-1-ol (10 mg, 86 μmol, 1.00 equiv) in dichloromethane (1 mL) was cooled to 0 °C. Triphenylphosphine (33 mg, 130 μmol, 1.50 equiv) was added and the mixture was stirred until it turned into a homogeneous clear solution. *N*-bromosuccinimide (23 mg, 130 μmol, 1.50 equiv) was added at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. The dark reaction mixture was directly purified by filtration through a pad of silica gel (ϕ 1 cm, length 2 cm) and rinsed with pentane. The title compound was obtained as a colorless liquid (13.8 mg, 90%, contained pentane). R_f = 0.78 (pentane); $[\alpha]^{24}_D$ = +6.2 (*c* 0.98, $CHCl_3$, 98% ee); ^{1}H NMR (400 MHz, $CDCl_3$, TMS as internal standard) δ (ppm) 0.90 (d, *J* = 6.4 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3 H), 1.12 (ddd, *J* = 13.6, 8.2, 6.4 Hz, 1 H), 1.22−1.38 (m, 1 H), 1.67 (dqqd, *J* = 7.6, 6.6, 6.6, 6.5 Hz, 1 H), 1.89 (m, 1 H), 3.32 (dd, *J* = 9.7, 6.3 Hz, 1 H), 3.42 (dd, *J* = 9.7 Hz, 4.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.0, 23.2, 25.4, 27.0, 33.0, 42.0, 44.4. These spectroscopic data are in agreement with those reported.[37]

(2*R*,4*S*)-2,4-Dimethylpentane-1,5-diol. A suspension of (3*R*,5*S*)-3,5-dimethyldihydro-2*H*-pyran-2,6(3*H*)-dione (**25**) (100 mmol, 14.3 g, 1.00 equiv) in diethyl ether (300 mL) was cooled to 0 °C. Lithium aluminum hydride (200 mmol, 7.59 g, 2.00 equiv) was added in portions under vigorous stirring over 1 h. The suspension was allowed to warm to room temperature overnight. The reaction mixture was cooled again to 0 °C, and water (8 mL), aqueous sodium hydroxide solution (15%, 8 mL), diethyl ether (100 mL), and water (24 mL) were added successively. The reaction mixture was stirred until it turned from gray to white (about 2 h) and dried over sodium sulfate. The solvent was removed *in vacuo* to obtain the title compound as a colorless, viscous, and hygroscopic oil (13.0 g, 98%). R_f = 0.28 (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$, TMS as internal standard) δ (ppm) 0.94 (ddd, *J* = 14.2, 7.1, 7.1 Hz, 1 H) 0.95 (d, *J* = 6.7 Hz, 6 H), 1.53 (ddd, *J* = 13.7, 6.8, 6.8 Hz, 1 H), 1.74 (ddqdd, *J* = 7.0, 6.8, 6.7, 5.7, 5.7, 2 H), 1.87 (br s, 2 H), 3.48 (d, *J* = 5.7 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 17.6 (2 C), 33.1 (2 C), 37.0, 67.9 (2 C). These spectroscopic data are in agreement with those reported.[38]

(2*S*,4*R*)-5-Hydroxy-2,4-dimethylpentyl Acetate (26). A solution of (2*R*,4*S*)-2,4-dimethyl-pentane-1,5-diol (2.00 g, 15.1 mmol, 1.00 equiv) in tetrahydrofuran (20 mL) was cooled to 0 °C. At this temperature Amano Lipase AK (110 mg) and vinyl acetate (2.10 mL, 1.95 g, 22.7 mmol, 1.50 equiv) were added. The reaction mixture was stirred for 30 min at 0 °C and 7 h at 5 °C. The enzyme was removed by suction filtration through Celite and washed with diethyl ether (40 mL). The homogeneous filtrate was concentrated *in vacuo*. This crude product was either directly used in the next reaction or for analytical purposes purified by flash chromatography (diethyl ether, ϕ 5 cm, length 16 cm, fraction size 40 mL, fractions 9−16) to obtain the clean title compound as a colorless oil (2.09 g, 79%). R_f = 0.42 (cyclohexane/ethyl acetate 1:1); $[\alpha]^{24}_D$ = +11.42 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS as internal standard) δ (ppm) 0.95 (d, *J* = 6.7 Hz, 3 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 1.00 (ddd, *J* = 13.8, 7.7, 7.1 Hz, 1 H), 1.45 (ddd, *J* = 13.7, 7.1, 6.6 Hz, 1 H), 1.52 (br s, 1 H), 1.74 (ddqdd, *J* = 7.7, 7.1, 6.7, 6.6, 5.5 Hz, 1 H), 1.90 (ddqdd, *J* = 7.1, 6.8, 6.7, 6.6, 5.4 Hz, 1 H), 2.06 (s, 3 H), 3.41 (dd, *J* = 10.3, 6.6, 1 H), 3.50 (dd, *J* = 10.3, 6.6, 1 H), 3.85 (dd, *J* = 10.8, 6.8, Hz, 1 H), 3.97 (dd, *J* = 10.8, 5.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 17.2, 17.8, 20.9, 30.0, 33.0, 37.3, 68.0, 69.2, 171.3. These spectroscopic data are in agreement with those reported.[39]

(2*S*,4*R*)-2,4-Dimethyl-5-(tosyloxy)pentyl Acetate (27). A solution of (2*S*,4*R*)-5-hydroxy-2,4-dimethylpentyl acetate (**26**) (1.70 g, 9.76 mmol, 1.00 equiv) in dry pyridine (30 mL) was cooled to 0 °C. Then *p*-toluenesulfonyl chloride (2.79 g, 14.6 mmol, 1.50 equiv) was added stepwise. The reaction mixture was allowed to warm to room temperature overnight. It was quenched by the addition of water (50 mL), followed by extraction with diethyl ether (3 × 40 mL). The organic layers were combined and washed with saturated aqueous copper(II) sulfate solution (2 × 60 mL), saturated aqueous sodium hydrogen carbonate (30 mL), and brine (30 mL). The solution was dried over sodium sulfate and concentrated *in vacuo*. This crude product was either directly used in the next step or for analytical purposes purified by flash chromatography (cyclohexane/ethyl acetate 1:1, ϕ 5 cm, length 18 cm, fraction size 40 mL, fractions 7−10) to obtain the title compound as a colorless oil (3.10 g, 97%, 97% ee). R_f = 0.52 (cyclohexane/ethyl acetate 1:1); $[\alpha]^{24}_D$ = +1.61 (*c* 1.24, $CHCl_3$; 97% ee); HPLC Chiralcel OJ-H column, heptane/ethanol 75:25, flow rate = 0.8 mL/min, 23 °C, detection at 230 nm, t_1 = 15.37 min (major), t_2 = 20.83 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$, TMS as internal standard) δ (ppm) 0.90 (d, *J* = 6.7 Hz, 3 H), 0.92 (d, *J* = 6.7 Hz, 3 H), 1.00 (ddd, *J* = 13.9, 7.4, 7.4 Hz, 1 H), 1.39 (ddd, *J* = 13.8, 6.9, 6.9, Hz, 1 H), 1.79 (dqddd, *J* = 7.4, 6.8, 6.8, 6.8, 6.8 Hz, 1 H), 1.89 (qdddd, *J* = 6.7, 6.7, 6.7, 6.2, 5.4 Hz, 1 H), 2.04 (s, 3 H), 2.45 (s, 3 H), 3.79 (dd, *J* = 10.8, 6.5 Hz, 1 H), 3.80 (dd, *J* = 9.5, 6.2 Hz, 1 H), 3.87 (dd, *J* = 10.7, 5.4 Hz, 1 H), 3.88 (dd, *J* = 10.6, 5.3 Hz, 1 H), 7.33−7.37 (m, 2 H), 7.76−7.81 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 17.1, 17.4, 20.9, 21.6, 29.8, 30.3, 36.9, 68.8, 74.7, 127.8 (2 C), 129.8 (2 C), 133.1, 144.7, 171.1. These spectroscopic data are in agreement with those reported.[40]

(2*S*,4*S*)-2,4,6-Trimethylheptan-1-ol (28). Lithium chloride (42 mg, 1.0 mmol, 0.60 equiv) and copper(II) chloride (68 mg, 0.50 mmol, 0.30 equiv) were flame-dried in a flask and dissolved in tetrahydrofuran (10 mL) to obtain an orange solution of lithium tetrachlorocuprate(II) (0.1 M in tetrahydrofuran).

A solution of (2*S*,4*R*)-2,4-dimethyl-5-(tosyloxy)pentyl acetate (**27**) (1.01 g, 3.07 mmol, 1.00 equiv) in tetrahydrofuran (20 mL) was cooled to −78 °C. The lithium tetrachlorocuprate(II) solution (0.1 M in tetrahydrofuran, 10 mL, 1.0 mmol, 0.30 equiv) was added via syringe. After 10 min an isopropylmagnesium bromide solution (1.0 M in tetrahydrofuran, 15.4 mL, 15.4 mmol, 5.00 equiv) was added via cannula. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was then cooled to 0 °C, and lithium aluminum hydride (117 mg, 3.07 mmol, 1.00 equiv) was added. It was again allowed to warm to room temperature overnight. The reaction mixture was cooled to 0 °C and quenched by the addition of saturated ammonium chloride solution (50 mL). Tetrahydrofuran was removed *in vacuo*. The residue was taken up in diethyl ether (50 mL). The phases were separated, and the aqueous phase was extracted with diethyl ether (4 × 50 mL). If

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no good phase separation was observed, some sodium potassium tartrate was added. The combined organic phases were washed with brine (30 mL), dried over sodium sulfate, and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/diethyl ether 1:1, ϕ 4 cm, length 20 cm, fraction size 25 mL, fractions 22−28) or short path distillation (10 mbar, 120−130 °C oil bath temperature) to obtain the title compound as a colorless oil (88 mg, 80%). R_f = 0.18 (cyclohexane/ethyl acetate 9:1); $[\alpha]^{24}_D = -16.3$ (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS as internal standard) δ (ppm) 0.84 (d, *J* = 6.5 Hz, 3 H), 0.86 (d, *J* = 6.6 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.92 (d, *J* = 6.7 Hz, 3 H), 0.89−0.99 (m, 2 H), 1.11 (ddd, *J* = 13.7, 8.9, 5.0 Hz, 1 H), 1.27 (ddd, *J* = 13.6, 6.8, 6.8 Hz, 1 H), 1.49 (br s, 1 H), 1.50−1.79 (m, 3 H), 3.37 (dd, *J* = 10.5, 6.8 Hz, 1 H), 3.53 (dd, *J* = 10.5, 5.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 17.3, 20.5, 22.0, 23.7, 25.2, 27.7, 33.0, 41.6, 46.5, 68.4. These spectroscopic data are in agreement with those reported.[41]

(2*S*,4*S*)-1-Bromo-2,4,6-trimethylheptane ((−)-19). A solution of (2*S*,4*S*)-2,4,6-trimethylheptan-1-ol (**28**) (800 mg, 5.05 mmol, 1.00 equiv) in dichloromethane (10 mL) was cooled to 0 °C. Triphenylphosphine (1.99 g, 7.60 mmol, 1.50 equiv) was added at once, and the mixture was stirred until it became a homogeneous solution. *N*-Bromosuccinimide (1.35 g, 7.60 mmol, 1.50 equiv) was added in portions over 15 min at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. The dark reaction mixture was concentrated *in vacuo*, purified by filtration through a pad of silica gel (ϕ 5 cm, length 10 cm), and rinsed with pentane. The title compound was obtained as a colorless liquid (1.06 g, 96%) by removal of the solvent. R_f = 0.78 (pentane); $[\alpha]^{24}_D = -2.16$ (*c* 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS as internal standard) δ (ppm) 0.85 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.93−1.13 (m, 3 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 1.37 (ddd, *J* = 13.6, 6.9, 6.7 Hz, 1 H), 1.48−1.61 (m, 1 H), 1.60−1.71 (m, 1 H), 1.83−1.96 (m, 1 H), 3.31 (dd, *J* = 9.8, 6.3 Hz, 1 H), 3.41 (dd, *J* = 9.8, 6.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.5, 20.2, 22.2, 23.5, 25.2, 27.7, 32.4, 41.7, 43.0, 46.7. These spectroscopic data are in agreement with the reported data of the enantiomeric compound.[42]

***tert*-Butyldiphenyl((4*S*,6*S*,8*S*,*E*)-4,6,8,10-tetramethylundec-2-enyloxy)silane ((+)-23).** Magnesium powder (330 mg, 14 mmol, 5.0 equiv) was suspended in diethyl ether (5 mL) and etched with dibromoethane (0.1 mL). Then the solvent was removed via syringe from the suspension. The etching process was repeated three times. Diethyl ether (5 mL) and one drop of dibromoethane were added (about 20 μL) to the remaining magnesium powder. Then (2*S*,4*S*)-1-bromo-2,4,6-trimethylheptane ((−)-**19**) (600 mg, 2.71 mmol, 1.20 equiv) was added over 20 min and stirred for 30 min at room temperature. A syringe was charged with the Grignard suspension.

A separate flask was charged with copper(I) bromide dimethyl sulfide complex (232 mg, 1.13 mmol, 0.500 equiv), (*R*,*E*)-1-(*tert*-butyldiphenylsilyloxy)pent-3-en-2-yl 2-(diphenyl-phosphino)benzoate ((*R*)-(+)-**6**) (1.42 g, 2.26 mmol, 1.00 equiv), and diethyl ether (50 mL). The Grignard suspension was added via a syringe pump over 1.25 h and stirred for another 1.5 h. The reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (petroleum ether, ϕ 5 cm, length 19 cm, fraction size 45 mL, fractions 6−12) to obtain the title compound as a colorless oil (0.99 g, 80%, *dr* > 95:5 by NMR). R_f = 0.25 (petroleum ether); $[\alpha]^{24}_D = +3.00$ (*c* 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS as internal standard) δ (ppm) 0.79 (d, *J* = 6.5 Hz, 3 H), 0.83 (d, *J* = 6.5 Hz, 3 H), 0.85 (d, *J* = 6.5 Hz, 6 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 0.81−0.98 (m, 3 H), 1.05 (s, 9 H), 1.08−1.31 (m, 3 H), 1.42−1.72 (m, 3 H), 2.17−2.29 (m, 1 H), 4.15−4.17 (m, 2 H), 5.44−5.56 (m, 2 H), 7.34−7.44 (m, 6 H), 7.65−7.71 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.2, 20.2, 20.3, 21.7, 22.1, 23.6, 25.2, 26.9 (3 C), 27.4, 27.5, 33.9, 44.4, 46.1, 46.8, 64.7, 127.1, 127.6 (2 C), 129.5 (4 C), 134.0 (2 C), 135.6 (4 C), 136.9. These spectroscopic data are in agreement with the reported data of the enantiomeric compound.[25]

(4*S*,6*S*,8*S*,*E*)-4,6,8,10-Tetramethylundec-2-en-1-ol ((+)-5). To a solution of *tert*-butyldiphenyl((4*S*,6*S*,8*S*,*E*)-4,6,8,10-tetramethylundec-2-enyloxy)silane ((+)-**23**) (200 mg, 430 μmol, 1.00 equiv) in tetrahydrofuran (3 mL) was added tetrabutylammonium fluoride trihydrate (407 mg, 1.30 mmol, 3.00 equiv) at room temperature. After 4.5 h TLC showed complete conversion. The reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/*tert*-butyl methyl ether, ϕ 3 cm, length 17 cm, fraction size 25 mL, fractions 21−27) to obtain the title compound as a colorless oil (96 mg, 98%). R_f = 0.15 (petroleum ether/ethyl acetate 9:1); $[\alpha]^{24}_D = +9.89$ (*c* 2.81, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS as internal standard) δ (ppm) 0.80 (d, *J* = 6.5 Hz, 3 H), 0.83 (d, *J* = 6.5 Hz, 3 H), 0.84 (d, *J* = 6.6 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 6.69 Hz, 3 H), 0.85−1.01 (m, 3 H), 1.04−1.19 (m, 2 H), 1.28 (ddd, *J* = 13.9, 9.5, 4.6 Hz, 1 H), 1.34 (br s, 1 H), 1.46−1.59 (m, 2 H), 1.60−1.69 (m, 1 H), 2.20−2.32 (m, 1 H), 4.08−4.11 (m, 2 H), 5.51 (dddd, *J* = 15.4, 7.9, 1.1, 1.1 Hz, 1 H), 5.61 (dddd, *J* = 15.4, 5.6, 5.6, 0.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 20.3, 20.3, 21.5, 22.1, 23.6, 25.2, 27.5, 27.5, 34.0, 44.3, 46.0, 46.8, 63.9, 127.3, 139.1. These spectroscopic data are in agreement with the reported data of the enantiomeric compound.[25]

((2*R*,3*R*)-3-((2*S*,4*S*,6*S*)-4,6,8-Trimethylnonan-2-yl)oxiran-2-yl)methanol ((+)-4b). *tert*-Butyl hydroperoxide (about 4 M in decane, 0.25 mL, about 4 equiv) was diluted with dichloromethane (0.75 mL) and dried over 4 Å ground molecular sieves for 2 h. A Schlenk flask was charged with titanium tetraisopropoxide (20 μL, 68 μmol, 0.25 equiv) and dichloromethane (2 mL) and dried over 4 Å ground molecular sieves for 1.5 h. (4*S*,6*S*,8*S*,*E*)-4,6,8,10-Tetramethylundec-2-en-1-ol ((+)-**5**) (60.0 mg, 0.275 mmol, 1.00 equiv) was dissolved in dichloromethane (1 mL) and dried over 4 Å ground molecular sieves for 30 min. The titanium tetraisopropoxide was cooled to −20 °C and stirred for another 30 min. Then D-(−)-diisopropyltartrate (17 μL, 81 μmol, 0.30 equiv) was added. After 30 min the solution of the allyl alcohol was added slowly over 10 min. Directly afterward the *tert*-butyl hydroperoxide solution was added, and the reaction mixture was stirred overnight at −20 °C (about 20 h, TLC shows full conversion).

The reaction mixture was quenched at −20 °C by addition of a solution containing iron(II) sulfate heptahydrate (3.3 g), citric acid (1.1 g), and water (10 mL). The mixture was stirred vigorously and allowed to warm to room temperature for 30 min, followed by extraction with diethyl ether (3 × 8 mL) and drying over sodium sulfate. Purification by flash chromatography (petroleum ether/diethyl ether 8:2, ϕ 2 cm, length 20 cm, fraction size 10 mL, fractions 26−31) to obtain the title compound as a colorless oil (54 mg, 83%, dr 90:10 determined by ^{1}H NMR). R_f = 0.18 (cyclohexane/ethyl acetate 8:2); $[\alpha]^{24}_D = +16.27$ (*c* 8.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS as internal standard) δ (ppm) 0.82 (d, *J* = 6.5 Hz, 3 H), 0.84 (d, *J* = 6.5 Hz, 3 H), 0.86 (d, *J* = 6.5 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.84−0.97 (m, 2 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 1.02−1.18 (m, 3 H), 1.36 (ddd, *J* = 13.7, 8.6, 5.2 Hz, 1 H), 1.44−1.51 (m, 1 H), 1.51−1.69 (m, 3 H), 1.72 (br s, 1 H), 2.68 (dd, *J* = 7.7, 2.4 Hz, 1 H), 2.99 (ddd, *J* = 4.5, 2.5, 2.5 Hz, 1 H), 3.61 (dd, *J* = 12.5, 3.7 Hz, 1 H), 3.92 (dd, *J* = 12.5, 2.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 18.0, 20.4, 20.6, 22.0, 23.7, 25.2, 27.4, 27.5, 32.9, 41.5, 45.8, 46.6, 58.5, 60.6, 61.8. These spectroscopic data are in agreement with the reported data of the enantiomeric compound.[25]

(2*S*,3*R*,4*S*,6*S*,8*S*)-2,4,6,8,10-Pentamethylundecane-1,3-diol ((−)-24b). Copper(I) cyanide (223 mg, 2.49 mmol, 3.00 equiv) was suspended in diethyl ether (10 mL) and cooled to −78 °C. A solution of methyl lithium (about 1.5 M in diethyl ether, 5 mL, 6

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equiv) was slowly added. The solution was stirred for 20 min at −78 °C. Then ((2*R*,3*R*)-3-((2*S*,4*S*,6*S*)-4,6,8-trimethylnonan-2-yl)-oxiran-2-yl)methanol ((+)-**4b**) (dr 90:10, 201 mg, 0.829 mmol, 1.00 equiv) dissolved in diethyl ether (5 mL) was added slowly. The solution was stirred for 1 h at −78 °C and allowed to warm to room temperature overnight. The reaction was cooled down to 0 °C, quenched with saturated ammonium chloride solution (20 mL), and stirred vigorously for 10 min. Then aqueous ammonia solution (about 25%, 5 mL) was added, and the mixture was stirred until the aqueous phase turned into a light blue (about 5−20 min). The phases were separated, and the aqueous phase was extracted with ethyl acetate (4 × 25 mL). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/diethyl ether 1:1, ϕ 4 cm, length 18 cm, fraction size 30 mL, fractions 30−42) to obtain the title compound as a colorless oil (209 mg, 97%, major diastereomer 189 mg). R_f = 0.52 (diethyl ether, major diasteromer); R_f = 0.47 (diethyl ether, minor diasteromer); $[\alpha]^{24}_D$ = −4.48 (*c* 0.87, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS as internal standard) δ (ppm) 0.82 (d, *J* = 6.9 Hz, 3 H), 0.84 (d, *J* = 6.7 Hz, 3 H), 0.84 (d, *J* = 6.5 Hz, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.84−0.96 (m, 2 H), 0.99 (ddd, *J* = 13.6, 8.0, 6.8 Hz, 1 H), 1.11 (ddd, *J* = 13.7, 9.0, 4.9 Hz, 1 H), 1.18 (ddd, *J* = 13.5, 7.2, 6.3 Hz, 1 H), 1.37 (ddd, *J* = 13.7, 7.8, 6.0 Hz, 1 H), 1.52−1.70 (m, 3 H), 1.73−1.84 (m, 1 H), 1.83−1.95 (m, 1 H), 2.38 (br s, 2 H), 3.47 (dd, *J* = 9.1, 2.5 Hz, 1 H), 3.67 (dd, *J* = 10.7, 7.8 Hz, 1 H), 3.73 (dd, *J* = 10.7, 3.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 12.9, 13.5, 20.5, 20.6, 22.0, 23.8, 25.2, 27.0, 27.6, 32.0, 37.5, 41.4, 45.9, 46.5, 69.0, 79.5. These spectroscopic data are in agreement with the reported data of the enantiomeric compound.[10]

(2*R*,3*R*,4*S*,6*S*,8*S*)-3-Hydroxy-2,4,6,8,10-pentamethylundecanoic Acid (29). To a solution of (2*S*,3*R*,4*S*,6*S*,8*S*)-2,4,6,8,10-pentamethylundecane-1,3-diol ((−)-**24b**) (8.0 mg, 31 μmol, 1.0 equiv) in dichloromethane (4 mL) were added saturated sodium hydrogen carbonate solution (20 mL) and sodium bromide (about 4 mg). The suspension was cooled to 0 °C. At this temperature 2,2,6,6-tetramethylpiperidine-1-oxyl free radical (about 4 mg) and after 5 min aqueous sodium hypochlorite (0.01 M, 4.0 mL) were added. After 25 min of stirring at 0 °C, TLC showed complete conversion. At 0 °C the reaction was quenched with saturated sodium thiosulfate solution (25 mL) and allowed to warm to room temperature. The reaction mixture was extracted with ethyl acetate (5 × 8 mL), dried over sodium sulfate, and concentrated *in vacuo*. The crude aldehyde ((2*R*,3*R*,4*S*,6*S*,8*S*)-3-hydroxy-2,4,6,8,10-pentamethylundecanal) (R_f = 0.79 (diethyl ether)) was used in the next step without any further purification.

Preparation of the Stock Solution. *tert*-Butanol (1.6 mL), 2-methyl-2-butene (purity 80%, 0.7 mL), sodium chlorite (28 mg), sodium dihydrogen phosphate (23 mg), and water (1.2 mL) were stirred vigorously in a small test tube for 10 min.

The freshly prepared stock solution was added to the aldehyde and stirred at room temperature for 3.5 h. Subsequently, the reaction mixture was diluted with water (8 mL) and extracted with ethyl acetate (5 × 8 mL). Purification by flash chromatography (cyclohexane/ethyl acetate 1:1 with 1% acidic acid, ϕ 1 cm, length 18 cm, fraction size 4 mL, fractions 21−27) to obtain the title compound as a viscous oil (6.5 mg, 78%). R_f = 0.26 (ethyl acetate); $[\alpha]^{24}_D$ = −8.00 (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS as internal standard) δ (ppm) 0.83 (d, *J* = 6.5 Hz, 3 H), 0.84 (d, *J* = 6.5 Hz, 3 H), 0.86 (d, *J* = 6.5 Hz, 3 H), 0.88 (d, *J* = 6.7 Hz, 6 H), 0.88−0.96 (m, 2 H), 1.00 (ddd, *J* = 13.7, 8.0, 6.8 Hz, 1 H), 1.10 (ddd, *J* = 13.7, 9.0, 4.9 Hz, 1 H), 1.13−1.19 (m, 1 H), 1.19 (d, *J* = 7.2 Hz, 3 H), 1.45 (ddd, *J* = 13.7, 7.6, 6.1 Hz, 1 H), 1.52−1.70 (m, 3 H), 1.77 (qdddd, *J* = 6.7, 6.5, 6.5, 6.5, 3.0 Hz, 1 H), 2.67 (dq, *J* = 8.6, 7.1 Hz, 1 H), 3.66 (dd, *J* = 8.7, 3.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 13.0, 14.0, 20.5, 20.6, 22.0, 23.8, 25.2, 27.0, 27.6, 31.5, 41.3, 43.3, 45.8, 46.5, 74.9, 181.0. These spectroscopic data are in agreement with the reported data of the enantiomeric compound.[25]

(+)-Vittatalactone ((+)-1b). A solution of (2*R*,3*R*,4*S*,6*S*,8*S*)-3-hydroxy-2,4,6,8,10-pentamethylundecanoic acid (**29**) (39.9 mg, 0.146 mmol, 1.00 equiv) in dry pyridine (0.4 mL) was cooled to 0 °C. *p*-Toluenesulfonyl chloride (57 mg, 0.29 mmol, 2.0 equiv) was added at once. The solution was allowed to warm to room temperature and stirred overnight. After TLC showed complete consumption of starting material (about 12 h) the reaction mixture was diluted with diethyl ether (10 mL) and water (10 mL). The phases were separated, and the aqueous phase was extracted with diethyl ether (3×10 mL). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (5 mL), dried over sodium sulfate, and concentrated *in vacuo* (200 mbar, 40 °C). Purification by flash chromatography (pentane/diethyl ether 9:1, ϕ 2 cm, length 16 cm, fraction size 5 mL, fractions 10−18) to obtain the title compound as a volatile colorless liquid (28.3 mg, 76%). R_f = 0.33 (pentane/diethyl ether 9:1); $[\alpha]^{24}_D$ = +1.2 (*c* 1.29, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, TMS as internal standard) δ (ppm) 0.84 (d, *J* = 6.6 Hz, 6 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.86−0.94 (m, 2 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 0.97−1.05 (m, 1 H), 1.10 (ddd, *J* = 13.6, 9.3, 4.5 Hz, 1 H), 1.16−1.34 (m, 2 H), 1.39 (d, *J* = 7.5 Hz, 3 H), 1.50−1.70 (m, 3 H), 1.87 (ddqd, *J* = 8.4, 8.4, 6.5, 5.0 Hz, 1 H), 3.25 (qd, *J* = 7.5, 4.1 Hz, 1 H), 3.87 (dd, *J* = 8.2, 4.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 12.9, 15.8, 20.8, 21.0, 21.8, 23.9, 25.2, 27.3, 27.7, 34.8, 39.8, 45.2, 46.0, 48.9, 83.8, 172.0. These spectroscopic data are in agreement with the reported data of the enantiomeric compound.[25]

Acknowledgment. This work was supported by the DFG, the International Research Training Group "Catalysts and Catalytic Reactions for Organic Synthesis" (IRTG 1038), the Fonds der Chemischen Industrie (fellowship to Y.S.), the Stiftung der Deutschen Wirtschaft (fellowship to K.L.), Novartis, and Wacker (Donation of Chemicals). We thank Prof. Dr. Wittcko Francke for sharing preliminary results, as well as G. Fehrenbach and Dr. M. Keller for analytical assistance and J. Weipert for synthetic work.

Supporting Information Available: Starting materials prepared by literature procedures and ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.