Synthesis and Stereochemistry of Some Bicyclic γ-Lactones from Parasitic Wasps (Hymenoptera: Braconidae). Utility of Hydrolytic Kinetic Resolution of Epoxides and Palladium(II)-Catalyzed Hydroxycyclization−Carbonylation−Lactonization of Ene-diols

Gregory C. Paddon-Jones,[†] Christopher S. P. McErlean,[†] Patricia Hayes,[†] Christopher J. Moore,[‡] Wilfried A. Konig,[§] and William Kitching*[,†]

Department of Chemistry, The University of Queensland, Brisbane, Q. 4072, Australia, Department of Primary Industries, Yeerongpilly, Q. 4105, Australia, and Institut fur Orgänische Chemie der Universität, D 20146, Hamburg, Germany

kitching@chemistry.uq.edu.au

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A palladium(II)-catalyzed hydroxycyclization−carbonylation−lactonization sequence with appropriate pent-4-ene-1,3-diols provides efficient access to the bicyclic γ-lactones, 5-*n*-butyl- and 5-*n*-hexyltetrahydrofuro-[3,2-*b*]furan-2(3*H*)-ones (**3**) and (**4**), respectively, in both racemic and enantiomeric forms. Some of the substrate pent-4-ene-1,3-diols of high enantiomeric excess (ee) have been derived from racemic terminal epoxides by hydrolytic kinetic resolution (HKR) using cobalt (III)−salen complexes. (9*Z*,12*R*)-(+)-Ricinoleic acid also serves as a "chiral pool" source of other pent-4-ene-1,3-diols. These syntheses and enantioselective gas chromatography confirm the structures and absolute stereochemistry of the lactones in some species of parasitic wasps (Hymenoptera: Braconidae). The highly abundant 5-*n*-hexyltetrahydrofuro-[3,2-*b*]furan-2(3*H*)-one (**4**) in *Diachasmimorpha kraussii* and *D. longicaudata* is of high ee (>99%) with (3a*R*,5*R*,6a*R*) stereochemistry.

Introduction

Certain species of parasitic wasps in the family Braconidae have been assessed for a possible role in integrated pest management strategies, particularly in fruit-fly control regimens, in Hawaii and eastern Queensland.[1−3] This approach, if adopted as a field strategy, requires the culturing and release of certified wasp populations. Consequently, there has been considerable interest in the morphology and taxonomy of these wasps,[4,5] which has experienced some uncertainty. This, for example, was the case[2,6] with *Diachasmimorpha kraussii* (Fullaway) which was previously described as *Opius kraussii*. This wasp is a natural enemy of the Queensland fruit-fly, *Bactrocera tryoni*, an aggressive pest with a very wide host range.

Our interest in fruit-fly chemistry and the likelihood that chemical profiling would assist taxonomic conclusions encouraged examination of the indigenous Australian species, *D. kraussii*, which is closely related to several braconid wasps previously investigated by Williams.[7] These authors reported that the Hagen's glands (located near the abdominal tips) of the braconid wasps, *D. longicaudata* (Ashmead), *D. tryoni* (Cameron), and *Fopius (Biosteres) arisanus*, are lactone and fragrance rich, and possible roles for these secretions have been discussed.[7] In addition to the known octan-4-olide (**1**) and dodecan-4-olide[8,9] (**2**), Williams[7] suggested that the novel and hitherto uncharacterized bicyclic lactones (**3**) and (**4**) ((3aα,5β,6aα)-5-*n*-butyl-tetrahydrofuro-[3,2-*b*]furan-2(3*H*)-one and 5-*n*-hexyl derivative, respectively) were also present. The structures and relative stereochemistry of **3** and **4** were based to a substantial degree,[7] on NMR comparisons with 5-*tert*-butyl-tetrahydrofuro[2,3-*b*]furan-2(3*H*)-one (**5**),[10] a useful but not ideal model. The relative configuration at C-5 (in **3** and **4**) was assigned using Karplus-based calculations of *vic*-^{1}H−^{1}H coupling constants. The absolute stereochemistry of **1**−**4** was not addressed (see Chart 1). All of the bicyclic lactones discussed in this paper are *cis* fused, and it is convenient to indicate relative stereochemistry by denoting the alkyl group at C-5 as either *cis* or *trans* to the *cis*-hydrogens at C-3a and C-6a.

Recently we outlined efficient syntheses of these lactones in both racemic and enantiomeric forms, together with the determination of their absolute stereochemistry.[11,12] After this brief report,[11] other syntheses of the Hagen's gland lactones **3** and **4** appeared[13−15] and in-

[†] The University of Queensland.
[‡] Department of Primary Industries.
[§] Institut fur Orgänische Chemie der Universität.

(1) Tryon, H. *Trans. Nat. Hist. Soc. Qld.* **1895**, *1*, 8.
(2) Rungrojwanich, K. Ph.D. Thesis (Entomology), 1994, The University of Queensland.
(3) Vargas, R. I.; Stark, J. D.; Nichida, G. K.; Purcell, M. *Environ. Entomol.* **1993**, *22*, 246 and references therein.
(4) Hagen, K. L. *Proc. Hawaii Entomol. Sci.* **1953**, *15*, 115.
(5) Buckingham, G. R. *Ann. Entomol. Soc. Am.* **1968**, *61*, 233.
(6) Wharton, R. A.; Marsh, P. M. *J. Washington Acad. Sci.* **1978**, *68*, 147.
(7) Williams, H. J.; Wong, M.; Wharton, R. A.; Vinson, S. B. *J. Chem. Ecol.* **1988**, *14*, 1727. (Since the report of Williams,[7] a reclassification of these wasps requires the names used in the present paper).
(8) Wheeler, J. W.; Happ, G. M.; Araujo, J.; Pasteels, J. M. *Tetrahedron Lett.*, **1972**, *46*, 4635.
(9) For an early summary of the occurrence of lactones in insects, Blum, M. S. *Chemical Defenses of Arthropods*; Academic Press: New York, 1981; especially Part I, Chapt. 9, and Part 18.
(10) Kohma, Y.; Kato, N. *Tetrahedron Lett.* **1979**, *48*, 4667.
(11) Paddon-Jones, G. C.; Moore, C. J.; Brecknell, D. J.; König, W. A.; Kitching, W. *Tetrahedron Lett.* **1997**, *38*, 3479.
(12) Paddon-Jones, G. C. Ph.D. Thesis, The University of Queensland, 1998.

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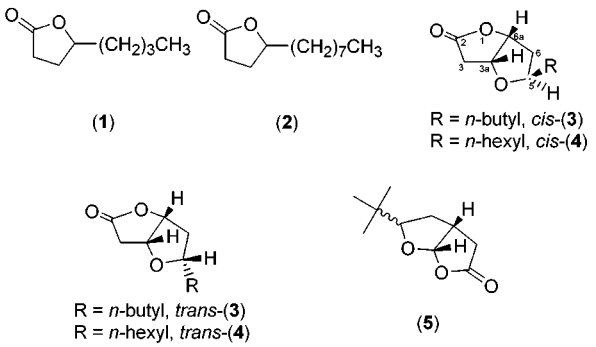
Chart 1



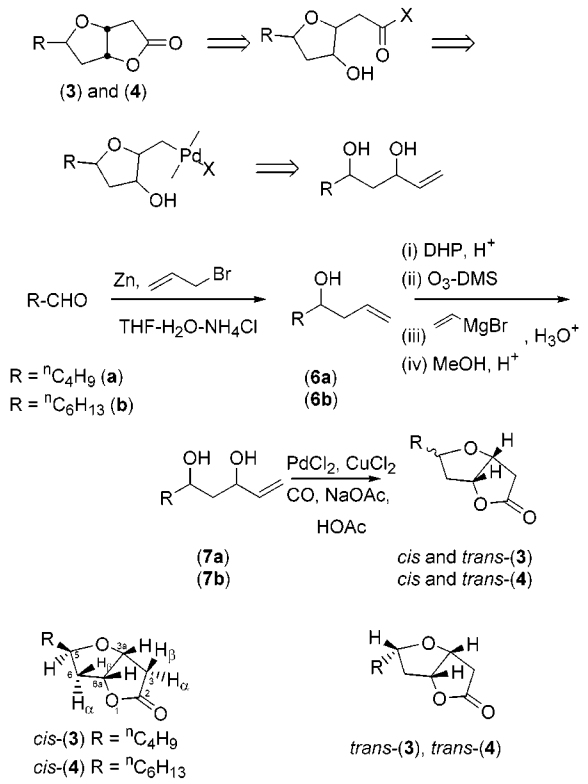
volved multistep sequences from carbohydrate precursors. In view of the interest in this family of lactones and the general utility of the palladium(II)-based manner of their construction,[16] we now describe our work in more detail. Furthermore, we demonstrate that hydrolytic kinetic resolution of terminal epoxides[17] provides simple access to precursors, that with the Pd(II)-catalyzed oxycarbonylation−lactonization sequence, deliver enantiomers of *cis* and *trans* **3** and **4**. The bicyclic lactone core of **3** and **4** is of further interest as it is a key substructure in a number of marine derived metabolites, including the plakortones.[18,19]

Results and Discussion

The simple γ-lactones **1** and **2** are well-known,[9] and we previously described[11] routes to their enantiomers. Enantioselective gas chromatography[20] established that **1** and **2** are *R*-configured (>99% ee), in agreement with considerable precedent for natural γ-lactones.[20−22] More detailed discussions are available elsewhere.[9]

Synthesis of Racemic Bicyclic γ-Lactones. The bicyclic lactones *cis*-**3** (~8%) and *cis*-**4** (92%) were concluded by Williams[7] to be present in *D. longicaudata*, and our examination of *D. kraussii* revealed the presence of the suspected **4** as a major component in that species.[11,12] We noted in **3** and **4** the presence of the lactone and tetrahydrofuran moieties and considered an approach based on metal ion induced ring closure of a suitable hydroxy alkene to deliver the tetrahydrofuran unit, followed by reaction of the presumed intermediate primary carbon−metal bond. Carbonylation was particularly attractive,[16] and the early work of Semmelhack[23] and later reports by Jäger[24] with carbohydrate-based enepolyols suggested that appropriate pent-4-ene-1,3-diols would be suitable starting materials. This plan is shown above, in Scheme 1, and the trial procedure was conducted with racemic, diastereomeric diols **7**, derived from either *n*-pentanal or *n*-heptanal.

Scheme 1

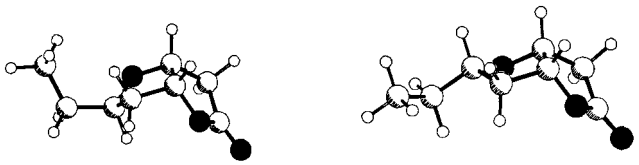


The reaction of the ene-diols **7a**,**b** was allowed to proceed overnight under the CO atmosphere, and the completed reaction was beige colored, in contrast to the initial bright green. After workup, GC-MS examination of each series showed two products in comparable amounts, with similar GC retention times and mass spectra. The apparent molecular ion ($M^+ = 184$ for R= *n*-C_4H_9 and 212 for R= *n*-C_6H_{13}), base peak (*m*/*z* 127, $M^+ - R$) and other ions, matched the data reported by Williams.[7] On the basis of *cis* ring fusion, the reaction products were considered to be the *cis* and *trans* isomers of **3** and **4** shown above (Scheme 1).

Confirmation of the structure and assignment of the relative stereochemistry of the suspected lactones **3** and **4** followed from a detailed analysis of the NMR spectra of the pairs of isomers, which could be separated either by careful flash chromatography or HPLC. The ^{1}H NMR spectra of the *n*-butyl isomers **3** although quite similar, do exhibit significant differences in some chemical shifts and coupling constants. The full ^{1}H and ^{13}C NMR assignments are listed in the Experimental Section. The major differences concern H6α and H6β which reverse their order of shifts in the isomeric pairs, with that proton located *syn* to the side-chain (H6β in (*cis*)) and H6α in

(13) Mereyala, H. B.; Gadikota, R. R. *Chem Lett.* **1999**, 273.
(14) Mereyala, H. B.; Gadikota, R. R.; Sunder, K. S.; Shailaja, S. *Tetrahedron* **2000**, *56*, 3021.
(15) Mereyala, H. B.; Gadikota, R. R. *Tetrahedron: Asymmetry* **2000**, *11*, 743.
(16) For pertinent reviews, see Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA 1994 and references therein.
(17) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421 and references therein.
(18) Patil, A. D.; Freyer, A. J.; Bean, M. F.; Carte, B. K.; Westley, J. W.; Johnson, R. K. *Tetrahedron* **1996**, *52*, 377.
(19) For synthetic endeavours in the plakortone area, see (a) Bittner, C.; Burgo, A.; Murphy, P. J.; Sung, C. H.; Thornhill, A. J. *Tetrahedron Lett.* **1999**, *40*, 3455. (b) Paddon-Jones, G. C.; Hungerford, N. L.; Hayes, P.; Kitching, W. *Org. Lett.* **1999**, *1*, 1905. (c) Semmelhack, M. F.; Shanmugam, P. *Tetrahedron Lett.* **2000**, *41*, 3567. (d) For synthesis of (−)-*trans*-kumausyne, see Boukouvalas, J.; Fortier, G.; Radu, I.-I. *J. Org. Chem.* **1998**, *63*, 916.
(20) For a discussion of enantioselective gas chromagrographic studies of lactones, see König, W. A. *Gas Chromatographic Enantiomer Separation with Modified Cyclodextrins*; Huthig: Heidelberg, 1992; especially pp 86−92.
(21) Schöttler, M.; Boland, W. *Helv. Chim. Acta* **1996**, *79*, 1448.
(22) Reference 20, Figure 75.
(23) (a) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496. (b) Semmelhack, M. F.; Kim, C.; Zhang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure Appl. Chem.* **1990**, *62*, 2035.
(24) Gracza, T.; Hasenöhvl, T.; Stahl, V.; Jäger, V. *Synthesis* **1991**, 1108.

Chart 2



***Cis*-lactone** ***Trans*-lactone**

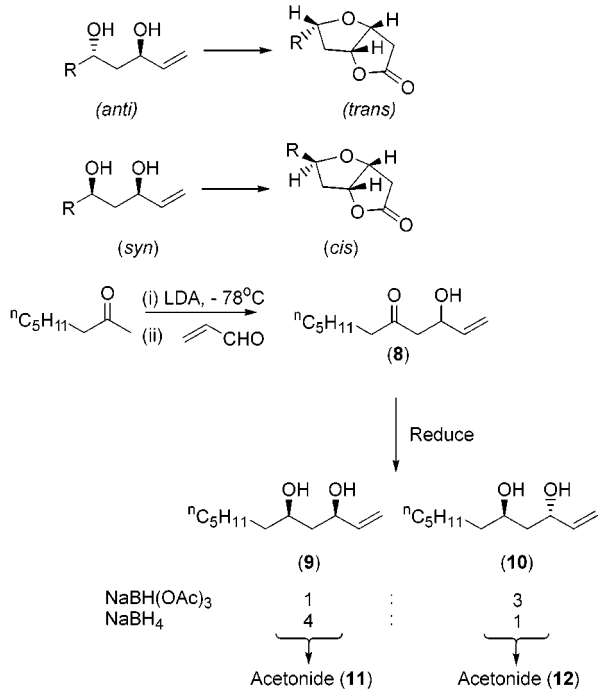
(*trans*)) appearing at higher field. The assignments and relative configurations of these racemic compounds were consistent with results from 1D-NOE experiments, and fully confirmed by NOESY results on individual enantiomers that were acquired later.

Model structures were computer-simulated and energy-minimized by the MM3 force field,[11,12] to provide estimates of dihedral angles, coupling constants, and general geometry, and permit comparisons with the experimental data. The minimized structures are shown above for the simpler ethyl derivatives (Chart 2), with the comparisons of computed and measured coupling constants (^3J) and dihedral angles being listed in the Supporting Information. In each isomer, the alkyl side chain is pseudo-equatorial, and for the *cis*-isomer, experimental and computed coupling constants match very well, but the comparisons are inferior for the *trans*-isomer, for which more than one conformer may be significantly populated. The NMR and mass spectral data, when compared with the published data[7] for the lactones from *D. longicaudata*, confirm that the natural bicyclic lactones are the *cis*-isomers **3** and **4**. (We synthesized and characterized the *cis* and *trans* isomers of the 5-(4′-pentenyl) lactone system in the hope of obtaining a crystalline metal-complex, e.g., with Pt(II), but this was not successful).[12]

Directed Synthesis of *Cis* and *Trans* Lactones 3 and 4. Consideration of the likely events in the conversion of pent-4-ene-1,3-diols to the bicyclic γ-lactones indicates that a *syn*-1,3-diol would provide the *cis*, and an *anti*-1,3-diol the *trans*-lactones as summarized below. (A demonstration of this is contained in a 1985 report by Yoshida,[25] who established the relative stereochemistry of their starting diols by NMR analysis of the acetonide derivatives).

The kinetic enolate from 2-octanone (LDA/THF) was quenched with acrolein to yield the hydroxyketone **8**. Reduction with $NaBH(OAc)_3$ in benzene (reflux) or in $HOAc-CH_3CN$ provided the same diol mixture on the basis of stereochemical analysis of the derived acetonide. GC-MS examination showed two components, the *anti*- and *syn*-acetonides in a 3:1 ratio. Use of $NaBH_4$ alone in benzene favored the *syn* isomer by ca. 4:1, as shown in Scheme 2. The acetonides were readily separated (HPLC), and using the ^{13}C NMR criterion emphasized by Rychnovsky,[26] the *syn*-acetonide **11** (δCH_3 30.1, 19.7 (DEPT)) was readily distinguished from the *anti* **12** (δCH_3 25.3, 26.4). Regeneration of the diols **9** and **10** from their acetonides (PPTS/MeOH) was followed by the Pd(II)-catalyzed process to yield the bicyclic lactones (*trans*- and *cis*-**4**). The *syn*-1,3-diol **9** produced exclusively the lactone previously deduced to be *cis*-**4** by the NMR criteria, and *anti*-1,3-diol **10** produced the isomeric *trans*-**4**. Consequently, the relative stereochemistry of the isomers **3** and **4** is established.

Scheme 2



In the original report[7] of the insect lactones, the 500 MHz ^1H NMR spectrum of "component 6" (acetone-d_6 solvent) was reproduced, and the ^1H and ^{13}C NMR shifts and coupling constants were tabulated. Comparisons with our data for the authentic *cis*- and *trans*-lactones **3** and **4**, confirm that both natural isomers have *cis*-relative stereochemistry as suggested.[7] The question of the absolute stereochemistry of the natural lactones was not considered, and our determination of this crucial feature is now described for both *D. longicaudata* and *D. kraussii*.

Enantiomers of Bicyclic Lactones 3 and 4. Normal gas chromatographic examination of the racemic bicyclic lactones was uncomplicated, and we considered that enantioselective gas chromatography was a promising approach for determination of the chirality of the natural lactones. Preliminary examination of the racemates of the *cis* and *trans* lactones **3** and **4** described above, using a noncommercial cyclodextrin based phase (see later), confirmed this, and so acquisition of enantiomerically enriched samples of the lactones was required for the salient comparisons to be made.

From (9*Z*,12*R*)-(+)-Ricinoleic Acid to the (3a*R*,5*R*,-6a*R*)- and (3a*S*,5*R*,6a*S*)-5-*n*-Hexyl-tetrahedrofuro-[3,2-*b*]furan-2(3*H*)-ones (4). This sequence commenced with conversion of the commercially available ricinoleic acid (**13**) to its methyl ester, followed by protection of the 12-hydroxyl group as the tetrahydropyran-2′-yl ether **14**.[27,28] Ozonolysis in methanol produced the *R*-configured aldehyde[29] which was immediately treated with an excess of vinylmagnesium bromide in THF (−40 °C) to

(25) Tamara, Y.; Kobayashi, T.; Kanamura, S.; Ochiai, H.; Hojo, M.; Yoshida, Z. *Tetrahedron Lett.* **1985**, 26, 3207.

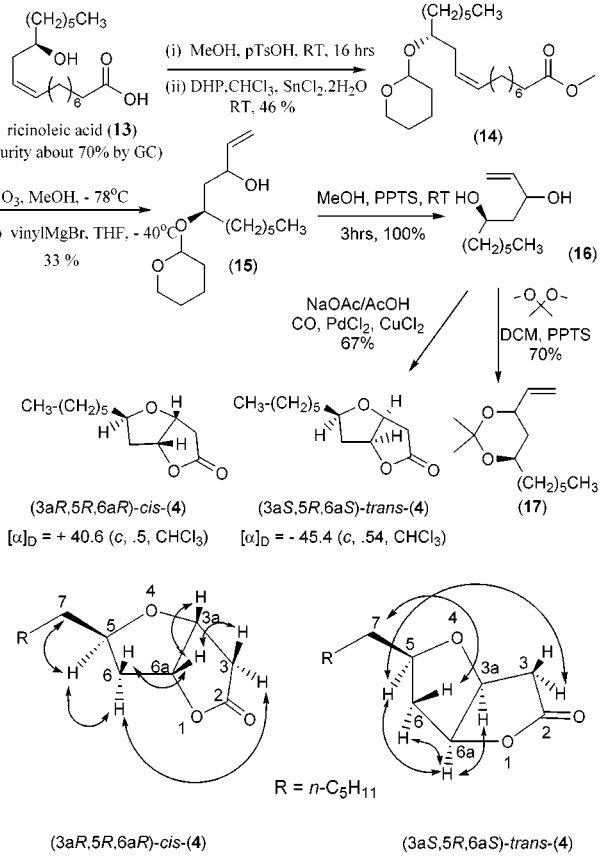
(26) Rychnovsky, S. D.; Slzalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945.

(27) D'Auria, M.; DeMico, A.; D'Onofrio, F.; Scettri, A. *Synthesis* **1985**, *10*, 988.

(28) Davis, K. J.; Bhalerao, V. T.; Rao, B. V. *Synth. Commun.* **1999**, *29*, 1679.

(29) (a) Kitching, W.; Lewis, J. A.; Perkins, M. V.; Drew, R. A. I.; Moore, C. J.; Schurig, V.; König, W. A.; Francke, W. *J. Org. Chem.* **1989**, *54*, 3893. (b) Kula, J.; Sikora, M.; Sadowska, H.; Piwowarski, J. *Tetrahedron* **1996**, *52*, 11, 321.

Scheme 3



provide protected ene-diol **15**. Deprotection released the (5*R*)-ene-diol **16** which could be converted to the separable *syn*- and *anti*-acetonides **17**, as described above for the racemate. The palladium(II)-catalyzed cyclization−carbonylation−lactonization sequence provided two isomeric lactones (~50:50, 67% overall) which were purified by HPLC. In this way, the *cis*- and *trans*-5-*n*-hexyl-tetrahydrofuro[3,2-*b*]furan-2(3*H*)-ones, with the (3a*R*,5*R*,6a*R*) and (3a*S*,5*R*,6a*S*) configurations, respectively, were acquired in six steps from the inexpensive, readily available ricinoleic acid. This procedure is shown above in Scheme 3. The relative configurations of the separated lactones were established by 2D-NOESY experiments, the main outcomes of which are summarized on the structures in Scheme 3. The absolute stereochemistry is enforced by the established (12*R*) configuration[29a] of the starting acid **13**, and this is not compromised during the procedure.

Utilizing Hydrolytic Kinetic Resolution of (±)-1,2-Epoxyhexane and (±)-1,2-Epoxyoctane. Jacobsen[17] has introduced a series of catalysts based on Co(salen) complexes that are effective for the hydrolytic kinetic resolution of terminal epoxides, and procedures incorporating such a step are finding increasing application in synthesis.[30] It appeared to us that this approach would be particularly useful for accessing the enantiomers of *cis*- and *trans*-**3** and **4**. This is possible because reconstituting the enantiomeric diol (the hydrolysis product from the racemic epoxide) provides the alternative epoxide enantiomer.

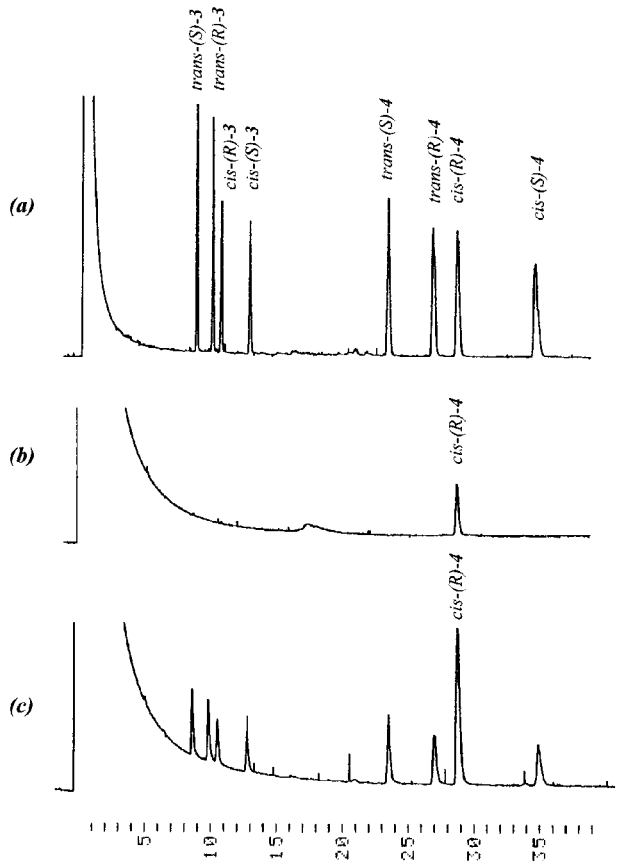


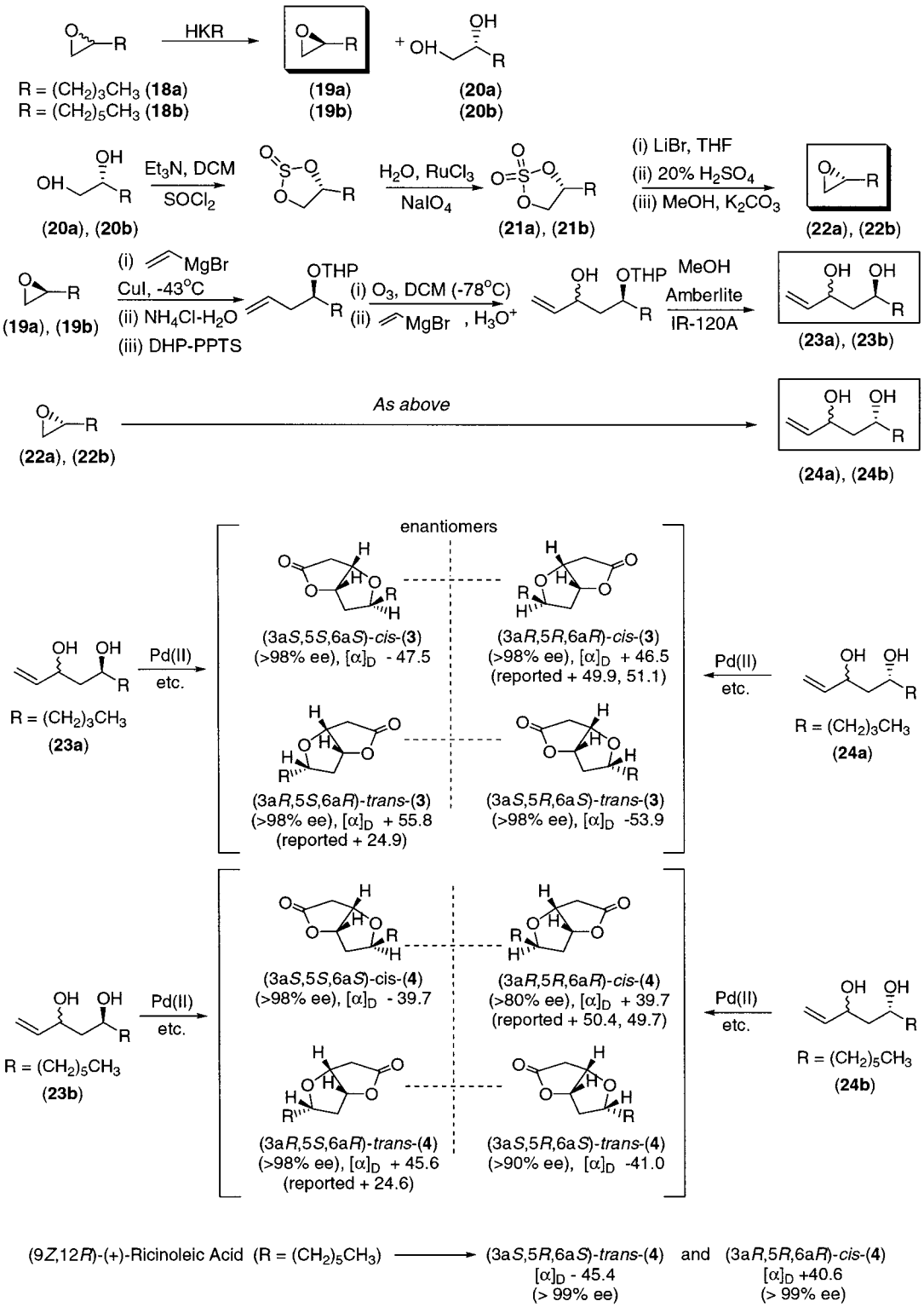
Figure 1. Enantioselective gas chromatographic analyses of Hagen's Gland lactone in *D. kraussii*. Column and conditions: 25 m capillary column with heptakis (6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)-β-cyclodextrin (50% dilution in polysiloxane OV 1701 w/w) at 160 °C, 0.5 bar H_2. (a) Enantiomers of the *cis*- and *trans*-5-*n*-butyl and 5-*n*-hexyl-lactones (**3** and **4**) (refer to Scheme 4). From shorter (at left) to longer retention times, signals correspond to 5*S* and 5*R* (*trans*) and 5*R* and 5*S* (*cis*) of the 5-*n*-butyl series then 5*S* and 5*R* (*trans*) and 5*R* and 5*S* (*cis*) of the 5-*n*-hexyl series. Under these conditions the eight signals have retention times from ca. 9 min (first eluting) to 35 min (last eluting). This order of elution was established by examination of the racemates and individual enantiomers of the lactone series, *cis*- and *trans*-5-*n*-butyl; *cis*- and *trans*-5-*n*-hexyl. (b) Trace of the lactone containing secretion from *D. kraussii*, showing a single isomer. (c) Coinjection of a and b demonstrating that the lactone in b is the (3a*R*,5*R*,6a*R*) (*cis*) isomer of the 5-*n*-hexyl series.

(±)-1,2-Epoxyhexane (**18a**) (from 1-hexene and *m*-chloroperbenzoic acid in DCM in the normal way) was subjected to hydrolytic kinetic resolution with (acetato)(aqua)(*S*,*S*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene-1,2-cyclohexanediamino)cobalt(III) in the manner described by Jacobsen.[17] Distillation of the reaction mixture (after 16 h) provided residual (*S*)-epoxide **19a** (~33%) and (*R*)-1,2-hexandiol (~40%), (**20a**). The (*R*)-diol **20a** was converted, via the cyclic sulfate **21a**,[31] to the (*R*)-epoxide **22a** in good yield. A similar procedure with (±)-1,2-epoxyoctane (**18b**) provided both (*S*)- and (*R*)-1,2-epoxyoctanes (**19b**) and (**22b**), respectively. These four epoxides were treated with vinyl MgBr−CuI to deliver the homoallylic alcohols which, as their THP-ethers, were ozonized and again reacted with vinylMgBr. Deprotection afforded the

(30) For very recent examples, see Chow, S.; Kitching, W. *Chem. Commun.* **2001**, 1040.

(31) (a) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538. (b) He, L.; Byun H-S.; Bittman, R. *J. Org. Chem.* **1998**, *63*, 5696.

Scheme 4



ene-diols (**23a**, **23b**, **24a**, **24b**), ready for the Pd(II)-catalyzed cyclization to the lactones. Flash chromatography and HPLC provided the suite of eight enantiomers of the *n*-butyl and *n*-hexyl lactones, which are shown in Scheme 4, along with isomeric relationships and optical rotations. NOESY spectra confirmed the relative stereochemistry of the *cis*- and *trans*-5-*n*-butyl lactones, as already shown in Scheme 3 for the 5-*n*-hexyl lactones, (3a*R*,5*R*,6a*R*)-*cis*-**4** and (3a*S*,5*R*,6a*S*)-*trans*-**4**.

The enantiomers of the synthesized *cis* and *trans* lactones (Schemes 3, 4) were well separated under enantioselective gas chromatographic conditions on a heptakis(6-*O*-TBDMS-2,3-di,*O*-methyl)-β-cyclodextrin - phase. The enantiomers of the *cis*-lactones were also well separated on a commercial γ-cyclodextrin column, but not the *trans*-isomers. The *cis* and *trans* lactones derived from ricinoleic acid (Scheme 4) were of >99% ee as anticipated, and the *cis*-isomers from the HKR route were >98% ee (3a*S*,5*S*,6a*S*, *n*-hexyl), >80% ee (3a*R*,5*R*,6a*R*, *n*-hexyl), >98%ee (3a*S*,5*S*,6a*S*, *n*-butyl), and >98% ee (3a*R*,5*R*,6a*R*, *n*-butyl). The *trans* lactones from the HKR route were estimated to be of >98% ee for (3a*R*,5*S*,6a*R*,

n-butyl), (3a*S*, 5*R*, 6a*S*, *n*-butyl), and (3a*R*,5*S*,6a*R*, *n*-hexyl) but of >90% ee for (3a*S*,5*R*,6a*S*, *n*-hexyl). Our measured rotations may be compared with those reported for the (3a*R*,6a*R*) series (see Scheme 4) acquired by longish routes from diacetone-D-mannose (~16 steps) or from diacetone-D-glucose.[13−15] The reported rotations are higher than ours for the *cis*-isomers, but significantly lower for the *trans*-isomers. It is worthy of emphasis that the eight enantiomers (all have *cis*-bicyclic fusion) of the *n*-butyl and *n*-hexyl lactones (Scheme 4) are available from the racemic 1,2-epoxyalkanes, using the HKR approach, by straightforward procedures involving relatively few steps, and one chromatographic separation of diastereomers.

With the availability of the racemates and enantiomers described above, enantioselective gas chromatography established that the (3a*R*,5*R*,6a*R*) (>99% ee) *cis*-*n*-hexyl lactone was present in *D. kraussii* and *D. longicaudata* (Figure 1). The latter species also contained the (3a*R*,5*R*,-6a*R*) *cis*-*n*-butyl lactone, and racemic *trans*-*n*-butyl lactone (3a*R*,5*S*,6a*R* and 3a*S*,5*R*,6a*S*) as minor components (~7% together). These determinations will now enable more detailed studies of the likely behavioral role of the lactones. In addition, further applications of these approaches to more complex bicyclic lactones are being conducted.[19b]

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 400 or 200 MHz with either TMS ($\delta = 0$) or the signal for residual $CHCl_3$ in the $CDCl_3$ solvent (δ 7.24) as internal standard. ^{13}C NMR spectra were recorded at 100 or 50 MHz with either TMS ($\delta = 0$) or the central peak of the $CDCl_3$ triplet (δ 77.00). *J* values are reported in hertz. Flash chromatography was performed with Kieselgel S (0.032−0.063 mm). Enantioselective gas chromatography was conducted using a permethylated γ-cyclodextrin column (SGE, 50 m, 0.25 μm) or heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)-β-cyclodextrin, 25 m (50% dilution in polysiloxane OV 1701 w/w) at 160 °C, 0.5 bar H_2.

(±)-Oct-1-en-4-ol (6a) and (±)-Dec-1-en-4-ol (6b). Pentanal (10 g, 116 mmol) and powdered zinc (8.5 g, ~130 mmol) were added to saturated aqueous NH_4Cl solution (100 mL) and THF (20 mL). A reflux condenser was fitted, and to the stirred contents was added allyl bromide (15.6 g, 130 mmol) dropwise. After addition was complete, stirring was continued at RT for 1 h, and then the reaction was quenched by addition of 10% aqueous HCl (50 mL). The resulting clear solution was extracted with ether, washed with brine, and dried ($MgSO_4$). Flash distillation afforded the homoallyl alcohol **6a** (10.3 g, 81 mmol, 70%) as a clear oil. ^{1}H NMR δ 0.86 (t, *J* 6.7, 3H), 1.20−1.90 (m, 7H), 2.05−2.28 (m, 2H), 3.59 (m, 1H), 5.09 (m, 2H), 5.82 (m, 1H). ^{13}C NMR δ14.1, 22.7, 27.5, 36.5, 41.9, 70.7, 118.1, 135.2. **Dec-1-en-4-ol (6b)** was prepared in a similar way from heptanal in 81% yield. ^{1}H δ 0.86 (t, *J* 6.5, 3H), 1.25 (m, 7H), 1.44 (m, 3H), 1.97 (brs, 1H), 2.12 (m, 1H), 2.23 (m, 1H), 3.57 (m, 1H), 5.10 (m, 2H), 5.78 (m, 1H). ^{13}C NMR δ 14.0, 22.5, 25.6, 29.3, 31.8, 36.4, 41.9, 70.7, 117.8, 134.9. These data match those reported previously.[32,33]

(±)-Non-1-ene-3,5-diol (7a). Homoallylic alcohol **6a** above (2.56 g, 20 mmol) was dissolved in dry DCM (25 mL) and dihydropyran (2.13 g, 25 mmol), and a catalytic amount of *p*-toluenesulfonic acid was added. The reaction was stirred overnight and then quenched by the addition of solid $NaHCO_3$. Filtration and solvent removal provided the crude diastereomeric **4-(tetrahydropyran-2′-yloxy)-1-octenes** which could be purified by chromatography on silica (EtOAc−hexane) (95%). ^{1}H δ 0.87 (t, *J* 7.0, 6H), 1.22−1.85 (m, 24H), 2.72 (m, 4H), 3.47 (m, 2H), 3.64 (m, 2H), 3.89 (m, 2H), 4.65 (dt, *J* 15.4, 2.8, 2H), 5.05 (m, 4H), 5.86 (m, 2H). ^{13}C NMR δ 14.1, 19.8, 22.8, 22.83, 25.4, 25.5, 27.3, 27.8, 31.0, 31.1, 33.1, 34.5, 38.0, 39.8, 62.6, 75.3, 76.7, 96.8, 98.1, 116.5, 116.9, 134.8, 135.5. Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.22; H, 11.45. The above THP-ether (330 mg, 1.55 mmol) was dissolved in DCM (30 mL) and cooled to −78 °C, and ozone was bubbled through until a blue color persisted. After purging with N_2, dimethyl sulfide (1.3 mL, 18 mmol) was added, and the reaction was allowed to warm to RT over 1 h. The solution was washed with brine and dried ($MgSO_4$), and the solvent was removed. The crude aldehyde was characterized by GCMS (*m*/*z* 214 (M^+, 1), 196 (0.5), 157 (0.6), 101 (36), 95 (40), 85 (100)) and then dissolved in dry THF (5 mL) and cooled to −78 °C. Vinylmagnesium bromide (Aldrich) (3 mL of 1 M, 3 mmol) was slowly added and after 2 h the reaction was quenched by the addition of saturated NH_4Cl solution (5 mL). Extraction (Et_2O, 2 × 5 mL), drying ($MgSO_4$), and solvent removal provided an oil which was purified by flash chromatography (30% Et_2O−hexane) to provide a mixture of four diastereomers of **3-hydroxy-5-(tetrahydropyran-2′-yloxy)non-1-ene** (315 mg, 84%). ^{1}H NMR δ0.87 (t, *J* 7.2, 12H), 1.23−1.76 (m, 56H), 3.44−4.92 (m, 24H), 5.05 (m, 4H), 5.25 (m, 4H), 5.84 (m, 4H). ^{13}C NMR (four diastereomers) δ 14.0, 19.7, 19.9, 20.7, 21.7, 22.8 (3C), 25.1, 25.4, 27.0, 27.3, 27.6, 27.7, 31.1, 31.2, 31.4 (2C), 34.3, 34.7, 35.2, 35.5, 39.3, 41.3, 41.9, 42.1, 62.9, 63.0, 63.3, 64.2, 65.6, 67.9, 69.6, 71.9, 72.5, 74.3, 75.9, 76.9, 77.2, 78.8, 98.0, 98.7, 99.3, 100.7, 113.3, 113.6, 113.9, 114.2, 140.7, 140.8, 140.9, 141.1. Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81 Found: C, 69.16; H, 10.80. The above diastereomeric mixture of THP-ethers (130 mg, 0.53 mmol) was dissolved in MeOH (15 mL), and amberlite IR-120 resin (250 mg) was added. After stirring overnight, the solution was filtered through Celite, and the solvent was removed to provide the diol **7a** (80 mg, 95%). ^{1}H NMR δ 0.85 (t, *J* 6.8, 6H), 1.25−1.63 (m, 16H), 3.08−3.85 (m, 6H), 4.29−4.53 (m, 2H), 5.05 (dd, *J* 15.1, 10.5, 2H), 5.20 (t, *J* 15.6, 2H), 5.83 (m, 2H). ^{13}C NMR δ 14.0 (2C), 22.5, 22.6, 27.4, 27.8, 37.1, 37.7, 42.2, 42.8, 69.0, 70.3, 72.3, 73.6, 114.1, 114.2, 140.7 (2C).

Undec-1-ene-3,5-diol (7b). The procedure described above for the conversion of oct-1-en-4-ol (**6a**) to non-1-ene-3,5-diol (**7a**) was applied to dec-1-en-4-ol (**6b**) for transformation to undec-1-ene-3,5-diol (**7b**). Protection of **6b** provided **4-(tetrahydropyran-2′-yloxy)-1-decene**. ^{1}H NMR δ 0.86 (t, *J* 6.7, 6H), 1.20−1.80 (m, 26H) 2.19−2.61 (m, 8H), 3.47−3.90 (m, 8H), 4.56−4.70 (m, 2H), 5.00−5.07 (m, 4H), 5.81 (m, 2H). ^{13}C NMR δ14.1 (2C), 19.8 (2C), 22.6, 22.7, 25.5, 25.6, 29.3, 29.4, 29.5, 29.6, 30.9, 31.1, 31.8, 31.9, 33.4, 34.8, 37.9, 39.8, 62.5, 62.6, 75.4, 76.7, 96.8, 98.1, 116.5, 116.9, 134.9, 135.5. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.15, H, 12.15. Ozonolysis followed by addition of vinylmagnesium bromide provided **3-hydroxy-5-(tetrahydropyran-2′-yloxy)undec-1-ene** as a diastereomeric mixture. ^{1}H NMR δ0.87 (t, *J* 6.7, 12H), 1.08−1.82 (m, 64H), 2.14−2.87 (m, 12H), 3.47−4.72 (m, 24H), 5.06 (m, 4H), 5.24 (m, 4H), 5.85 (m, 4H). ^{13}C NMR δ14.0 (2C), 14.1, 19.9 (2C), 20.7, 21.7, 22.6 (2C), 22.7, 24.8, 25.1, 25.2, 25.4 (2C), 25.6, 29.3, 29.4 (2C), 29.5, 29.6, 29.7, 31.1, 31.2, 31.4, 31.5, 31.8 (2C), 31.9, 34.6, 35.0, 35.5, 35.9, 39.6, 41.3, 41.9, 42.1, 62.9, 63.0, 64.2, 65.6, 65.8, 67.9, 69.7, 72.0, 72.5, 74.3, 75.9, 76.9, 77.2, 79.0, 98.0, 98.7, 99.3, 100.8, 113.3, 113.6, 113.9, 114.2, 140.8 (2C), 140.9, 141.1. Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.91; H, 11.23. The above THP-ether was deprotected as described above for **6b**, to provide undec-1-ene-3,5-diol (**7b**). ^{1}H NMR δ 0.86 (t, *J* 6.7, 6H), 1.15−1.83 (m, 22H), 2.35 (brs, 4H), 3.29−4.09 (m, 4H), 4.35−4.84 (m, 2H), 5.10 (m, 2H), 5.28 (m, 2H), 5.85 (m, 2H). ^{13}C NMR δ14.0 (2C), 22.5, 25.3, 25.6, 25.7, 29.2, 29.25, 31.7, 31.8, 37.4, 38.2, 42.8, 42.9, 68.9, 69.1, 72.3, 73.4, 114.4, 114.5, 140.6 (2C). (In another preparation of this diol, a derivative acetonide was characterized and is described later in this section). This diol was then ready for transformation to the bicyclic lactone.

(32) Davis, A. P.; Jaspars, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2111.

(33) Jones, P.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 186.

***cis*- and *trans*-5-*n*-Butyltetrahydrofuro[3,2-*b*]furan-2(3*H*)-ones**: *cis*-**3** and *trans*-**3**. The following is a representative procedure for the hydroxycyclization−carbonylation−lactonization sequence. Non-1-ene-3,5-diol (**7a**) and undec-1-ene-3,5-diol (**7b**) to the bicyclic lactones **3** and **4**, respectively.

NaOAc (3 equiv) and $CuCl_2$ (3 equiv) were added to a dry three-necked flask containing ∼10 mL glacial acetic acid. The solution was stirred until the solid dissolved, and then the unsaturated diol (1 equiv) was added as an acetic acid solution. The flask was then purged several times with nitrogen while the contents were vigorously stirred, which ensured the inertness of the atmosphere in the flask. Carbon monoxide was added from an attached balloon, and the system was flushed several times with this gas. A catalytic amount of $PdCl_2$ (0.1 equiv) was then added, and stirring was continued under these conditions. After refilling the balloon with CO, the reaction was stirred overnight at room temperature. Generally this resulted in a change in color from bright green to a dull brown. The CO atmosphere was removed, and ∼50 mL H_2O was added which caused the solution to turn black. This solution was then neutralized with solid $NaHCO_3$ until effervescence ceased. Extraction of this neutralized solution with EtOAc, followed by removal of this solvent gave the crude bicyclic lactones. Flash chromatographic purification (15% Et_2O in hexane) resulted in a sample that was then subjected to HPLC (15% EtOAc−hexane) for separation of the isomeric lactones.

Treatment of non-1-ene-3,5-diol (**7a**) (80 mg, 0.5 mmol) in the above way provided 75 mg (81%) of a mixture of *cis*- and *trans*-**3** (ca. 50:50) which were purified and then separated by HPLC.

cis-**3**. ^{1}H NMR δ 0.84 (t, *J* 6.7, 3H, CH_3), 1.22 (m, 4H, $2CH_2$ in side-chain), 1.46 (m, 1H, in side-chain), 1.58 (m, 1H, in side-chain), 1.68 (ddd, *J* 13.7 (H6α), 10.1 (H5), 4.6, (H6a), 1H, H6*β*), 2.35 (dd, *J* 13.7 (H6*β*), 4.6 (H5), 1H, H6α), 2.62 (d, *J* 18.8 (H3*β*), 1H, H3α), 2.74 (dd, *J* 18.8 (H3α), 6.5 (H3a), 1H, H3*β*), 4.08 (m, 1H, H5), 4.79 (dt, *J* 6.5 (H3*β*), 4.6 (H6a), 1H, H3a), 5.09 (t, *J* 4.6 (H3a, H6*β*), 1H, H6a). ^{13}C NMR δ 13.9 (CH_3) 22.6 (CH_2), 28.1 (CH_2) 34.3 (CH_2), 36.6 (C3), 38.8 (C6), 77.3 (C5), 78.5 (C3a), 84.9 (C6a), 175.9 (C2). GCMS: *m*/*z* 184 (M^+, 1), 156 (1), 143 (2), 127 (100), 95 (3), 83 (7), 71 (20). HREIMS: $C_{10}H_{16}O_3$ requires 184.1099. Measured, 184.1099. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.81; H, 9.07.

trans-**3**. ^{1}H NMR δ 0.87 (t, *J* 6.4, 3H, CH_3), 1.25 (m, 4H, $2CH_2$ in side chain), 1.56 (m, 1H, in side chain), 1.62 (m, 1H in side chain), 1.85 (ddd, *J* 14.2 (H6*β*) 7.1 (H5), 2.3 (H6a), 1H, H6α), 2.40 (ddd, *J* 14.2 (H6α), 7.1 (H5), 6.7 (H6a), 1H, H6*β*), 2.69 (d, *J* 3.8, 2H, H3α, H3*β*), 3.91 (m, 1H, H5), 4.47 (brdd, *J* 4.4 (H6a), 3.8 (H3α, 3*β*), 1H, H3a), 4.98 (ddd, *J* 6.7 (H6*β*), 4.4 (H3a), 2.3 (H6α), 1H, H6a). ^{13}C NMR δ 13.9 (CH_3), 22.5 (CH_2), 28.2 (CH_2), 35.2 (CH_2), 36.4 (C3), 38.3 (C6), 78.2 (C5), 80.3 (C3a), 84.6 (C6a), 175.6 (C2). GCMS: *m*/*z* (184, M^+, 1), 156 (1), 143 (2), 127 (100), 83 (7), 71 (20).

cis-**4**. ^{1}H NMR δ0.85 (t, *J* 6.8, 3H, CH_3) 1.25 (m, 8H, 4 CH_2 in side chain), 1.48 (m, 1H in side-chain), 1.58 (m, 1H in side-chain), 1.65 (ddd, *J* 14.0 (H6α), 10.3 (H5), 4.7 (H6a), 1H, H6*β*), 2.35 (dd, *J* 14.0 (H6*β*), 4.8 (H5), 1H, H6α), 2.62 (d, *J* 18.8 (H3*β*), 1H, H3α), 2.73 (dd, *J* 18.8 (H3α), 6.7 (3Ha), 1H, H3*β*), 4.05 (m, *J* 10.3 (H6*β*), 4.8 (H6α), 1H, H5), 4.78 (dd, *J* 6.7 (H3*β*), 4.7 (H6a), 1H, H3a), 5.09 (dd, *J* 4.7 (H3a), 4.7 (H6*β*), 1H, H6a). ^{13}C NMR δ 14.0 (CH_3), 22.5 (CH_2), 26.0 (CH_2), 29.2 (CH_2) 31.7 (CH_2), 34.7 (CH_2), 36.6 (C3), 38.8 (C6), 77.3 (C5), 78.3 (C3a), 84.9 (C6a), 176.0 (C2). GCMS: *m*/*z* 212 (M^+, 1), 194 (1), 165 (1), 152 (1), 143 (5), 128 (6), 127 (100), 99 (26), 81 (10). HREIMS: $C_{12}H_{20}O_3$ requires 212.1412. Measured, 212.1415. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.54; H, 9.55.

trans-**4**. ^{1}H NMR δ 0.87 (t, *J* 6.0, 3H, CH_3), 1.25 (m, 8H, $4CH_2$ in side-chain), 1.56 (m, 1H in side-chain), 1.62 (m, 1H in side-chain), 1.85 (ddd, *J* 14.2 (H6*β*), 7.9 (H5), 2.3 (H6a), 1H, H6α), 2.40 (ddd, *J* 14.2 (H6α), 7.1 (H5), 6.7 (H6a), 1H, H6*β*), 2.69 (d, J 3.5 (H3a), 2H, H3α, H3*β*), 3.91 (m, J 7.9 (H6α), 7.1 (H6*β*) 1H, H5), 4.48 (dd, *J* 4.5 (H3α, H3*β*), 4.5 (H6a), 1H, H3a), 4.99 (ddd, *J* 6.7 (H6*β*), 4.5 (H3a), 2.3 (H6α), 1H, H6a). ^{13}C NMR δ 14.0 (CH_3), 22.5 (CH_2), 26.0 (CH_2), 29.1 (CH_2), 31.7 (CH_2), 34.7 (CH_2), 36.6 (C3), 38.3 (C6), 78.2 (C5), 80.4 (C3a), 84.7 (C6a), 175.4 (C2). GCMS: *m*/*z* 212 (M^+, 1), 194 (0.6), 165 (1), 152 (1), 143 (5), 127 (100), 99 (26), 81 (10), 55 (36), 43 (37).

3-Hydroxyundec-1-en-5-one (**8**). A solution of LDA in THF (50 mL of 0.17 M solution, 8.5 mmol) under N_2 was cooled to −78 °C, and a THF solution of 2-octanone (0.97, 7 mmol) was added slowly. After 1 h at −78 °C, a THF solution of acrolein (7 mmol, 0.4 g in 5 mL) was added, and after ca. 20 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl. The organic material was extracted into ether (2 × 15 mL) which was dried and evaporated. The target compound **8** was purified by flash chromatography (30% EtOAc/hexane) (1.80 g, 4.8 mmol, 68%). ^{1}H NMR δ0.84 (t, *J* 7.1, 3H, CH_3), 1.24 (m, 7H), 1.52 (m, 2H), 2.38 (t, *J* 7.4, 2H), 2.58 (m, 2H), 4.51 (brd, *J* 5.3 Hz, 1H), 5.08 (dt, *J* 10.5, 1.5, 1H), 5.23 (dt, *J* 17.2, 1.5, 1H), 5.80 (ddd, *J* 17.2, 10.5, 5.6, 1H). ^{13}C NMR δ 14.0, 22.4, 23.5, 28.8, 31.5, 43.7, 48.7, 68.6, 114.8, 139.1, 211.4. GCMS: *m*/*z* (184, M^+, 1), 166 (1), 155 (1), 127 (2), 113 (19), 96 (4), 86 (6), 71 (11), 43 (100). HREIMS: $C_{11}H_{20}O_2$ requires 184.1463. Measured, 184.1468. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.99; H, 10.98. This compound **8** was previously characterized only by its ^{1}H NMR spectrum.[34]

Undec-1-ene-3,5-diol from Hydride Reductions: **9 and 10**. The above keto alcohol **8** was dissolved in benzene and added to a solution of sodium triacetoxyborohydride in benzene. The mixture was allowed to stir for 2h at RT and then quenched with water. Benzene was carefully removed, and the residue was taken up in ethyl acetate, washed with water and brine, and then dried ($MgSO_4$). Concentration yielded the crude diols in a 3:1 ratio, and this mixture was converted immediately into the acetonide derivatives. A second reduction procedure, utilizing the mixed solvent $CH_3COOH-CH_3CN$ at − 40 °C, was employed. Again the *anti*−*syn* ratio **10**:**9**, was ca. 3:1, whereas use of $NaBH_4$ in benzene at 20 °C favored the *syn* diol **9** (4:1). These relative stereochemistries were confirmed by examination of the acetonides. The diol mixture (30 mg, 0.16 mmol) and dimethoxypropane (∼0.3 mL) were dissolved in DCM (∼5 mL) along with a catalytic amount of PPTS (∼ 5 mg). This mixture was allowed to stir at RT for 4 h. The solution was washed with saturated $NaHCO_3$ solution, and the organic phase dried and concentrated. The acetonides were then subjected to HPLC separation, using 15% EtOAc−hexane, and this provided the *syn*- and *anti*-acetonides **11** and **12**. HREIMS: $C_{13}H_{23}O_2$ (M − CH_3) requires 211.1698. Measured, 211.1693.

***syn*-4-Hexyl-2,2-dimethyl-6-vinyl-[1,3]-dioxane** (**11**) (from **9**): ^{1}H NMR δ 0.85 (t, *J* 6.0, 3H, CH_3), 1.24−1.36 (m, 10H), 1.40 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.51−1.58 (dt, *J* 12.9, 2.6, 2H), 3.90 (m, 1H), 4.32 (m, 1H), 5.11 (dt, *J* 10.6, 1.5, 1H), 5.25 (dt, *J* 17.2, 1.5 1H), 5.80 (ddd, *J* 17.2, 10.4, 5.8, 1H). ^{13}C NMR δ 13.9, **19.7** (**CH_3**), 22.4, 24.7, 29.1, **30.1 (CH_3)**, 31.6, 36.3, 36.7, 68.6, 70.2, 98.4, 115.1, 138.8.

***anti*-4-Hexyl-2,2-dimethyl-6-vinyl-[1,3]-dioxane** (**12**) (from **10**): ^{1}H NMR δ 0.90, (t, *J* 6.8, 3H, CH_3) 1,20−1.40 (m, 10H), 1.26 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.58−1.65 (m, 2H), 3.92 (m, 1H), 4.46 (M, 1H), 5.20 (ddd, *J* 17.5, 2.0, 1.2, 1H), 5.29 (ddd, *J* 10.9, 2.2, 1.4, 1H), 6.00 (ddd, *J* 17.5, 10.9, 4.1, 1H). ^{13}C NMR δ 15.2, 21.2, 23.6, **24.6 (CH_3), 25.3 (CH_3),** 28.8, 30.2, 30.8, 38.8, 72.3 (2C), 100.3, 117.1, 137.6. Regeneration of the pure *syn*- and *anti*-undec-1-ene-3,5-diols **9** and **10**, respectively, was effected by treating each of the acetonides (100 mg, 0.45 mmol) in methanol with a catalytic amount of PPTS. The disappearance of the acetonide was followed by GC analysis. After 3 h, solid $NaHCO_3$ was added, the solution filtered, and solvent removal provided the enediols, which were characterized by their ^{13}C NMR spectra. *syn*-undec-1-ene-3,5-diol (**9**): ^{13}C NMR δ 13.9, 22.5, 25.1, 29.1, 31.6, 38.0, 42.8, 72.4, 73.7, 114.3, 140.6. *anti*-Undec-1-ene-3,5-diol (**10**) ^{13}C NMR δ 14.1, 25.6 (2C), 29.2, 31.8, 37.5, 42.2, 69.0, 69.2, 114.4, 140.7. These syn and *anti*-diols were converted to the *cis*- and *trans*-bicyclic lactones, respectively, as discussed in the text.

(34) Das, N. B.; Torssell, K. B. G. *Tetrahedron* **1983**, *39*, 2247.

Methyl (9*Z*,12*R*)-12-(Tetrahydropyran-2′-yloxy)ricinoleate (14). A solution of commercially available ricinoleic acid (**13**) (8 g, 18.8 mmol, 70% by GC) in methanol (50 mL) containing *p*-TsOH (15 mg) was stirred at room temperature for 15 h. The mixture was then concentrated, diluted with DCM, and washed with saturated aqueous $NaHCO_3$. After drying ($MgSO_4$) and concentration, the crude ester was obtained as an oil. This product[27] was used directly in the next step. GCMS: 294 ($M^+ - H_2O$, 1), 166 (21), 124 (15), 96 (27), 84 (30), 55 (100), 41 (58). The crude ester (3.43 g 11 mmol) was dissolved in chloroform (50 mL) along with dihydropyran (10 mL), and a catalytic quantity of $SnCl_2 \cdot 2H_2O$ (20 mg) was added. The mixture was stirred at RT for 4 h after which the solution was filtered and concentrated to give the protected methyl ester as an oil. This product was purified by flash chromatography (silica, Et_2O/hexane: 5/95) to give 2 g (46% from ricinoleic acid) of the pure ester **14** as a colorless oil. ^1H NMR δ 0.85 (t, *J* 7.1, 3H), 1.24−1.37 (m, 18H), 1.39−1.71 (m, 8H), 1.94−2.04 (m, 2H), 2.21−2.29 (m, 4H), 3.41−3.48 (m, 1H), 3.63 (s, 3H), 3.84−3.97 (m, 1H), 4.63 and 4.69 (2dd, *J* 2.8, 3.0, 1H), 4.84 (m, 1H), 5.26−5.46 (m, 2H). ^{13}C NMR δ 14.0, 22.5, 24.9, 25.3, 27.3, 29.1 (2C), 29.18, 29.2, 29.5, 31.7, 31.8, 31.0, 35.5, 34.0, 51.4, 73.6, 75.7, 96.7, 124.3, 132.5, 173.5. GCMS (*m*/*z* %): 294 (1), 263 (1), 101 (2), 85 (100), 67 (8), 55 (12), 43 (13). These spectral data matched those reported.[28]

5-(Tetrahydropyran-2′-yloxy)undec-1-en-3-ol (15). A solution of the methyl ester (**14**) of ricinoleic acid (2 g, 5 mmol) in methanol (100 mL) was cooled to −78 °C, and ozone was admitted in the until a light blue color persisted. Oxygen was then passed through the solution until it became colorless. The reaction mixture was treated with an excess of dimethyl sulfide (1 mL), warmed to RT, and stirred for 1 h. After concentration under reduced pressure, the crude aldehyde (about 2 g) was used without purification in the next step. GCMS (*m*/*z* %): 242 (M^+, 0.3), 157 (0.3), 141 (2.1), 123 (9.7), 101 (46.9), 85 (100), 81 (32.2), 67 (33.5), 57 (29.9), 56 (41.2), 55 (54.3), 43 (50.8), 41 (66.3). The crude aldehyde (∼2 g) in THF (60 mL) was cooled to −40 °C, and an excess of vinylmagnesium bromide (16 mL, 1 M in ether) was added dropwise. At the end of this addition, the solution was slowly warmed to RT and stirred for another 2 h. After quenching with an aqueous saturated solution of NH_4Cl, the solution was concentrated and the aqueous phase extracted with ethyl acetate (3 × 50 mL). The organic phase was washed with aqueous NaCl solution and then water and dried ($MgSO_4$). The residue was purified by flash chromatography (20% ether in hexane) to afford **15** (450 mg, 33%, mixture of four diastereomers) as a colorless oil. Anal. Calcd for $C_{16}H_{30}O_3$: C 71.07; H 11.18. Found C 70.91; H 11.23. GCMS (*m*/*z* %): 213 ($M^+ - CH_2{=}CH{=}CHOH$, 1), 185 (1), 151 (5), 109 (12), 101 (20), 95 (25), 85 (100).

First isomer: ^1H NMR δ 0.86 (t, *J* 7.0, 3H), 1.25−1.82 (m, 19H), 3.43−3.50 (m, 1H), 3.83−3.89 (m, 1H), 3.97−4.00 (m, 1H), 4.10 (brd, 3.4, 1H), 4.45−4.47 (m, 1H), 5.04 (dt, *J* 10.6, 1.6, 1H), 5.24 (dt, *J* 17.3, 1.6, 1H), 5.87 (ddd, *J* 17.3, 10.6, 5.2, 1H). ^{13}C NMR δ 14.1, 21.7, 22.6, 25.1, 25.4, 29.4, 31.5, 31.8, 35.5, 42.1, 65.6, 67.9, 74.3, 100.8, 113.3, 140.7. Mixture of three isomers: ^1H NMR δ 0.86 (t, *J* 7.0, 9H) 1.79−2.27 (m, 57H), 3.45−3.53 (m, 3H), 3.74−3.98 (m, 6H), 4.21−4.26 (m, 1H), 4.35−4.37 (m, 2H), 4.61−4.72 (m, 3H), 5.03−5.09 (m, 3H), 5.20−5.28 (m, 3H), 5.80−5.88 (m, 3H). ^{13}C δ 14.0 (3C), 19.9 (2C), 20.7, 22.6 (3C), 24.7, 25.1, 25.2, 25.3, 25.5, 29.4 (2C), 29.5, 31.1, 31.2, 31.4, 31.7, 31.8 (2C), 34.6, 35.0, 35.8, 39.6, 41.2, 41.9. 62.9, 63.0, 64.2, 69.7, 71.9, 72.5, 75.9, 76.8, 78.9, 98.0, 98.7, 99.3, 113.6, 113.9, 114.2, 140.8, 140.9, 141.1.

(5*R*)-Undec-1-ene-3,5-diol (16). A solution of the monotetrahydropyranyl ether **15** (218 mg, 0.8 mmol) in dry MeOH (30 mL) in the presence of Amberlite IR-120 (300 mg) was stirred at RT overnight. After filtration, drying ($MgSO_4$), and concentration, the pure diol **16** (150 mg, 100%) was obtained as a colorless oil. This material exhibited spectral properties that matched those listed above for diastereomers of this enediol system, and for the derived acetonides **11** and **12**.

(3a*R*,5*R*,6a*R*)-5-*n*-Hexyltetrahydrofuro[3,2-*b*]furan-2(3*H*)-one and (3a*S*,5*R*,6a*S*)-5-*n*-Hexyltetrahydrofuro-[3,2-*b*]furan-2(3*H*)-one (4). Following the general procedure, addition of the unsaturated 1,3-diol **16** (130 mg, 0.7 mmol) in acetic acid (2 mL) to a mixture of NaOAc (172 mg, 2.1 mmol, 3 equiv) and $CuCl_2$ (282 mg, 2.1 mmol, 3 equiv) in acetic acid (10 mL), in the presence of a catalytic amount of $PdCl_2$ (12 mg, 0.1 equiv), provided the crude bicyclic lactones **4**. Purification by flash chromatography afforded these lactones (100 mg, 67%, 50/50 mixture) as a colorless oil. Separation by HPLC (15% ethyl acetate in hexane) provided both pure lactones whose ^1H and ^{13}C NMR spectra and GCMS data matched these listed above. Anal. Calcd for $C_{12}H_{20}O_3$: C 67.89; H 9.50. Found: C 67.54; H 9.55. HREIMS (70 eV) $C_{12}H_{20}O_3$ requires 212.1412. Measured 212.1415. (3a*R*,5*R*,6a*R*)-*cis*-**4**: $[\alpha]^{22}_D$ + 40.6 (*c*, 0.5, $CHCl_3$); (3a*S*,5*R*,6a*S*)-*trans*-**4**: $[\alpha]^{22}_D$ −45.4 (*c*, 0.54, $CHCl_3$).

Hydrolytic Kinetic Resolution of (±)-1,2-Epoxyhexane (18a) and Synthesis of the (3a*S*,5*S*,6a*S*), (3a*R*,5*S*,6a*R*), (3a*S*,5*R*,6a*S*), and (3a*R*,5*R*,6a*R*) Stereoisomers of 5-*n*-Butyltetrahydrofuro[3,2-*b*]furan-2(3*H*)-one (3) (Scheme 4). Freshly generated catalyst, (acetato) (aqua) ((*S*,*S*)(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino)cobalt(III), from the commercial precursor (120 mg, 0.196 mmol)[35] was added to (±)-1,2-epoxyhexane (from 1-hexene and *m*-chloroperbenzoic acid in DCM in the normal way) (5 g, 50 mmol) and water (495 μL, 27.5 mmol). The slurry was stirred for 16 h and then subjected to distillation. Epoxide **19a** was collected at 120 °C (1 atm) (1.55 g, 31%) and 1,2-hexandiol (**20a**) at 118 °C (12 mmHg) (2.48 g, 42%). The recovered epoxide was identical spectroscopically with starting racemic material and exhibited $[\alpha]^{22}_D$ −7.5 (*c*, 2.2, $CHCl_3$) (reported[36] $[\alpha]^{22}_D$ −8.3 (*c*, 1.0, $CHCl_3$)).

(*S*)-(−)-1,2-epoxyhexane (**19a**) (1 g, 10 mmol) was dissolved in THF (3 mL) and added to a THF solution generated at −10 °C from CuI (76 mg, 0.4 mmol) and vinylmagnesium bromide (20 mL of 1 M solution, 20 mmol). The reaction was stirred and allowed to warm to 0 °C (2 h) and then quenched with saturated NH_4Cl solution. The ether extract (2 × 20 mL) was dried ($MgSO_4$) and the solvent removed under reduced pressure. The clear oil was purified by flash chromatography (10% DCM in hexane), to provide (*S*)-(−)-oct-1-en-4-ol, $[\alpha]^{22}_D$ −8.47 (*c*, 3.08, $CHCl_3$). Anal. Calcd for $C_8H_{16}O$:C, 74.94, H, 12.58. Found: C, 74.57; H, 12.54. This sample exhibited ^1H and ^{13}C NMR and mass spectra that matched those for the racemic alcohol **6a** described above. The tetrahydropyran-2′-yl ether was acquired as described above for the racemic alcohol and exhibited matching ^1H and ^{13}C NMR spectra. Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54, H, 11.39. Found: C, 73.22, H, 11.45. This protected (*S*)-(−)-oct-1-en-4-ol was ozonized and the resulting aldehyde treated with vinylmagnesium bromide as described for the racemic material to yield (*R*,*S*)-3-hydroxy-(*S*)-5-(tetrahydropyran-2′-yloxy)non-1-ene, which was deprotected as described previously to provide non-1-ene-3,5-diol (**23a**) (predominantly (5*S*)) which was converted to a mixture of the *cis*- and *trans*-5-*n*-butyltetrahydrofuro[3,2-*b*]furan-2(3*H*)-ones, with (3a*S*,5*S*,6a*S*) and (3a*R*,5*S*,6a*R*) stereochemistry, respectively, as described in detail above. The former isomer had $[\alpha]^{22}_D$ −47.5 (*c*, 1.46, $CHCl_3$), and the latter $[\alpha]^{22}_D$ +55.8 (*c* 1.18, $CHCl_3$). The ^1H and ^{13}C NMR spectra and mass spectra matched those described above for the racemic compounds.

(*R*)-Hexane-1,2-diol (**20a**) (1 g, 8.4 mmol) was dissolved in DCM (15 mL) and cooled to 0 °C. Triethylamine (4.7 mL, 33.6 mmol) was added and then thionyl chloride (920 μL, 12.6 mmol). After stirring for 5 min, the reaction was diluted with ether (50 mL), washed with water (2 × 30 mL), dried ($MgSO_4$), and filtered through Celite. The solvent was removed under reduced pressure and the crude sulfite taken up in a mixture of CH_3CN (30 mL) and H_2O (30 mL). $RuCl_3$ (20 mg, 0.1 mmol) and $NaIO_4$ (3.6 g, 16.8 mmol) were added, and the reaction was stirred for 2 h. The reaction mixture was diluted with ether (50 mL) and the aqueous phase extracted further with ether (2 × 30 mL). The combined ether phases were dried

(35) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

(36) Haase, B.; Schneider, M. *Tetrahedron: Asymmetry* **1993**, *4* (5), 1017.

($MgSO_4$), and the solvent was removed. The resulting sulfate **21a** was dried azeotropically with *i*-PrOH (15 mL) (1.22 g, 81%.). Anal. Calcd for $C_6H_{12}O_4S$: C, 39.99; H, 6.71. Found: C, 39.59; H, 6.87. ^{1}H NMR δ 0.89, (t, *J* 6.9, 3H, CH_3), 1.17−1.39 (m, 4H), 1.73 (m, 1H), 1.90 (m, 1H), 4.31 (t, *J* 8.4, 1H), 4.68 (dd, *J* 8.6, 5.9, 1H), 4.94 (m, 1H). ^{13}C NMR δ 13.6 (CH_3), 22.0 (CH_2), 26.5 (CH_2) 31.8 (CH_2) 72.9 (CH_2), 83.1 (CH). $[\alpha]^{22}_D$ +6.0 (*c*, 5.11, $CHCl_3$). This cyclic sulfate **21a** (250 mg, 1.39 mmol) in THF (3 mL) was treated with LiBr (480 mg, 5.6 mmol) and stirred for 3 h. The solvent was removed and the residue taken up in ether (5 mL) to which was added 20% H_2SO_4 (5 mL). After vigorous stirring (∼ 12 h), the mixture was extracted with ether (2 × 5 mL) and the organic phase dried ($MgSO_4$) and evaporated to provide the presumed crude bromohydrin. This was immediately dissolved in MeOH (5 mL) and cooled to 0 °C, and K_2CO_3 (775 mg, 5.6 mmol) was added. After 3 h, saturated NH_4Cl solution (15 mL) was added and the mixture extracted with DCM (3 × 10 mL) which was then dried ($MgSO_4$) and the solvent carefully removed. Flash chromatography (10% DCM in hexane) afforded the (*R*)-epoxide **22a** (42 mg, ∼30%). $[\alpha]^{22}_D$ + 3.9 (*c*, 0.6, $CHCl_3$). (This rotation is low, but a realistic measure of the ee of this volatile epoxide is indicated by the ee of the final bicyclic lactone.) This was processed, as described above in detail for its enantiomer **19a** to yield the (3a*R*,5*R*,6a*R*)-*cis*-**3** and (3aS,5R,6aS)-*trans*-(**3**) lactones, with $[\alpha]^{22}_D$ +46.5 and −53.9, respectively. The ^{1}H and ^{13}C NMR spectra of these matched those described for the racemic compounds.

Hydrolytic Kinetic Resolution of (±)-1,2-Epoxyoctane (18b) and Synthesis of the (3a*S*,5*S*,6a*S*), (3a*R*,5*S*,6a*R*), (3a*S*,5*R*,6a*S*), and (3a*R*,5*R*,6a*R*) Stereoisomers of 5-*n*-Hexyltetrahydrofuro[3,2-*b*]furan-2(3*H*)-one (4). The procedures described above commencing with (±)-1,2-epoxyhexane (**18a**) were followed with (±)-1,2-epoxyoctane (**18b**). From racemic epoxide (5.9 g, 46 mmol) and catalyst (120 mg, 0.2 mmol of precatalyst) were obtained (*S*)-(−)-1,2-epoxyoctane (**19b**) (128 °C at 226 mmHg, 1.91 g, 33%) and (*R*)-(+)-diol **20b** (120 °C at 6 mm Hg, 2.7 g, 40%, mp 35°). For (*S*)-(−)-epoxide **19b**. $[\alpha]^{22}_D$ −8.9 (*c*, 1.8, $CHCl_3$). Anal. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.62; H, 12.78. ^{1}H NMR δ 0.86 (t, *J* 7.0, 3H, CH_3), 1.22−1.53 (m, 10H), 2.43 (dd, *J* 5.1, 2.8, 1H), 2.71 (dd, *J* 5.0, 4.0, 1H), 2.88 (m, 1H). ^{13}C NMR δ 14.0 (CH_3), 22.5 (CH_2), 25.9 (CH_2), 29.1 (CH_2), 31.7 (CH_2) 32.5 (CH), 47.1 (CH_2), 52.4 (CH). Reaction of this epoxide with vinylmagnesium bromide in the presence of CuI afforded (*S*)-(−)-1-decen-4-ol: Anal. Calcd for $C_{10}H_{20}O$: C, 76.85; H, 12.91. Found: C, 77.06; H, 12.98. $[\alpha]^{22}_D$ −7.2 (*c*, 2.13, $CHCl_3$). The NMR spectral data were in agreement with those listed above for the racemate. This alcohol was protected in the normal way as its tetrahydropyran-2′-yl ether (Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.93; H, 11.75. Found: C, 75.15; H, 12.15), which provided NMR spectra matching those described above. Ozonolysis and reaction of the resulting aldehyde with vinylmagnesium bromide afforded (5*S*)-5-(tetrahydropyran-2′-yloxy)undec-1-en-3-ol spectroscopically consistent with the diastereomeric diol mixture described above. This was deprotected in the manner described to provide predominantly (5*S*)-undec-1-ene-3,5-diol (**23b**) identical with material characterized above.

This diol **23b** was then subjected to the Pd(II)-catalyzed lactone forming reaction and provided two lactones (59 mg, (93%) from 60 mg of starting diol, **23b**). These lactones were separated in the normal way (HPLC) to provide the (3a*S*,5*S*,-6a*S*)-*cis*-**4** and (3a*R*,5*S*,6a*R*)-*trans*-**4** lactones, with $[\alpha]^{22}_D$ −39.7 and $[\alpha]^{22}_D$ +45.6, respectively. The ^{1}H and ^{13}C NMR spectra matched those of the racemic compounds detailed above. The (*R*)-(+)-diol **20b** (1 g, 6.8 mmol) was converted to the cyclic sulfate **21b** in the manner described (1.0 g, 74% from diol). Anal. Calcd for $C_8H_{16}O_4S$: C, 46.14; H, 7.74. Found: C, 46.03; H, 7.88 $[\alpha]^{22}_D$ +7.1 (*c* 1.94, $CHCl_3$). ^{1}H NMR δ 0.87 (t, *J* 6.9, 3H, CH_3), 1.17−1.49 (m, 8H), 1.73 (m, 1H), 1.93 (m, 1H), 4.31 (t, *J* 8.4, 1H), 4.68 (dd, *J* 8.7, 6.0, 1H), 4.95 (m, 1H). ^{13}C δ 13.9 (CH_3), 22.4 (CH_2), 24.5 (CH_2), 28.6 (CH_2), 31.4 (CH_2), 32.2 (CH_2), 72.8 (CH_2), 82.9 (CH). This cyclic sulfate **21b** (300 mg, 1.44 mmol) was converted to the corresponding (*R*)-epoxide **22b** (90 mg, 49%) (as described for (*R*)-hexane-1,2-diol (**20a**)) $[\alpha]^{22}_D$ +7.4 (*c*, 4.5, $CHCl_3$). This epoxide **22b**, through the (5*R*)-undec-1-ene-3,5-diol, $[\alpha]^{22}_D$ +7.1 (*c*, 0.5, $CHCl_3$) (**24b**) was processed to the bicyclic lactones in the manner described in detail above, to provide the (3a*R*,5*R*,6a*R*)-*cis*-**4** and (3a*S*,5*R*,6a*S*)-*trans*-**4** lactones, with $[\alpha]^{22}_D$ +39.7 (*c*, 1.05, $CHCl_3$) and $[\alpha]^{22}_D$ −41.0 (*c*, 1.02, $CHCl_3$), respectively.

The bicyclic lactones prepared were separated into their enantiomers on a heptakis (6-*O*-TBDMS-2,3-di,*O*-methyl)-β-cyclodextrin phase (see text and Figure 1), whereas a commercially available γ-cyclodextrin phase separated the enantiomers of the *cis*-lactones but not those of the *trans*-lactones. The optical rotations, directly determined ee's (by gas chromatography, and comparisons of optical rotations) and the relationships between the various stereoisomers are shown in Scheme 4.

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Supporting Information Available: List of the computed and measured coupling constants and dihedral angles for the lactones in Chart 2 and copies of the enantioselective GC traces for *cis*-5-*n*-butyl-**3** and cis-*n*-hexyl-**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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