Total Synthesis of 3-Hydroxydrimanes Mediated by Titanocene(III) – Evaluation of Their Antifeedant Activity

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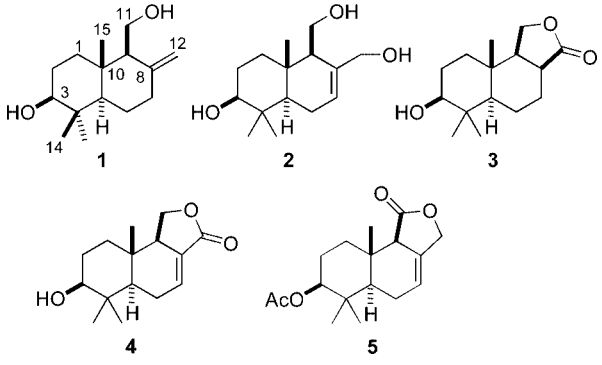
We describe the first synthesis of 3β-hydroxydihydroconfertifolin (**3**) and 3β-hydroxycinnamolide (**4**), together with improved procedures for the preparation of other 3-hydroxydrimanes (**2** and **5**) scarce in nature. The key step was the titanocene(III)-promoted cyclization of epoxypolyprenes, readily prepared from commercial polyenes. In this way, we confirm the viability of our procedure for the synthesis of drimane sesquiterpenoids with different functionalization patterns. We also report on the antifeedant activity of **2–5** against four insect species with different feeding ecologies.

Introduction

Among natural sesquiterpenoids,[1] 3-hydroxydrimanes are intriguing metabolites that occur in organisms such as plants, fungi, and nudibranchs,[2–12] which are philogenetically very distant but share the common feature of having an appetizing and apparently vulnerable appearance for predators. We therefore speculated that, as occurs with other closely related sesquiterpenoids,[13,14] these metabolites might act as chemical deterrents against insects and other parasites. Moreover, 3-hydroxydrimanes are considered to constitute a biochemical linkage between drimanes and rearranged drimanes,[15] and have proven to be useful building blocks for the synthesis of higher terpenoids of pharmacological interest.[16,17] Some of them are also cytotoxic, inhibitors of *myo*-inositol monophosphatase, and show other interesting biological properties.[18] These compounds have therefore attracted the attention of chemists, and been synthesized through the degradation of higher terpenoids,[19] by microbiologicallyassisted procedures,[20–22] and by light-induced[23] and acid-induced cyclization of epoxypolyprenes.[24] These procedures, however, are specific for only one or a few products and often require numerous steps or give low overall yields. The aim of our present work has been to confirm the viability of the titanocene(III)-based procedure recently developed in our laboratory for the synthesis of isodrimenediol (**1**)[25–27] for the production of other 3-hydroxydrimanes (**2**–**5**) with different functionalization patterns which are scarce in nature. We also considered that evaluation of their antifeedant activity might cast some light on the structure–activity relationships of these natural products.



Results and Discussion

As we had previously found, the titanocene(III)-catalyzed cyclization of epoxypolyprene **7**,[25] obtained from commercially available *all-trans*-farnesol (**6**) by van Tamelen's procedure,[28] gave a mixture from which the desired exocyclic alkene **8** [29] could be isolated in 40% yield (Scheme 1). Apart from **8**, we also isolated a minor quantity of the endocyclic regioisomer **9** [28] (7% yield).

Once we had the cornerstone intermediate **8** to hand, we undertook the synthesis of the natural drimane **2** (Scheme 2), found in the fungi *Marasmius oreades* [4] and *Polyporus arcularius*,[11] and previously prepared by chemobiological and semisynthetic procedures.[3,20,30] Our total synthesis of **2** began with the protection of the hydroxy group of **8** as a benzoyl ester, and subsequent treatment

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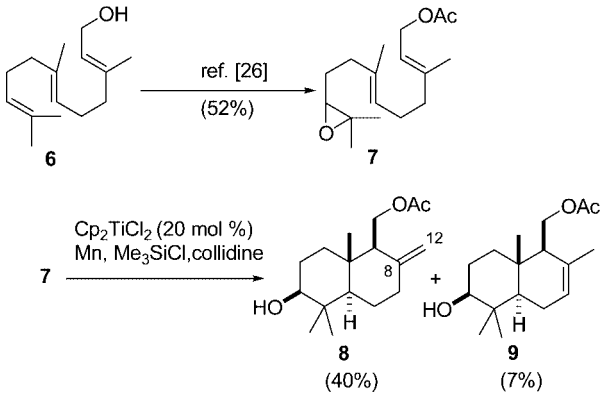
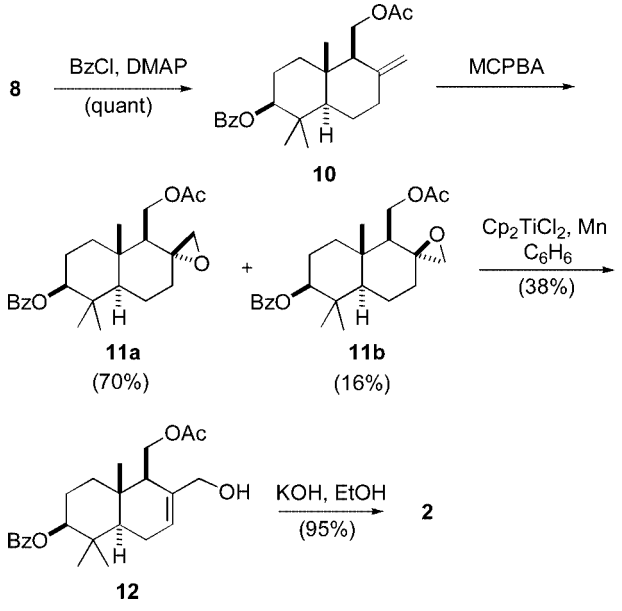


Scheme 1. Synthesis of the cornerstone intermediate **8**

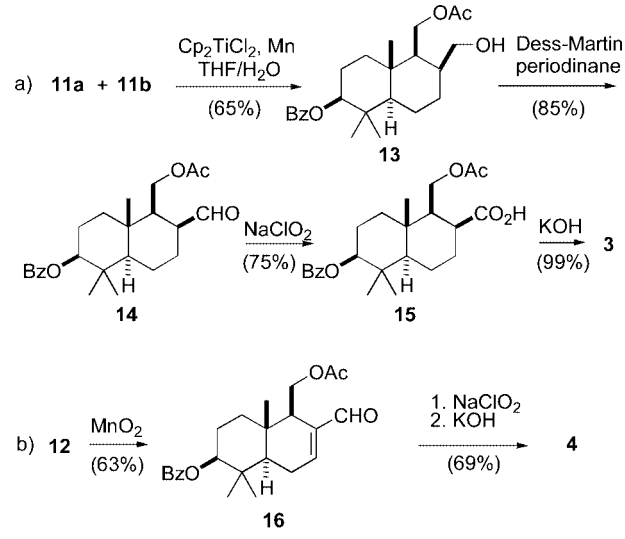
with MCPBA (Scheme 2), through which we obtained the epoxides **11a** and **11b** (roughly 4:1 ratio) in 86% combined yield. Different assays to open the oxirane ring of these products by treatment with either protic (TsOH) or Lewis (BF_3) acids, gave mixtures in which the desired alkene **12** was not detected.[31,32] On the other hand, titanocene(III)-promoted oxirane opening under anhydrous conditions furnished **12** in a moderate yield of 38% (from the epimeric mixture).[33,34] Finally, saponification of **12** provided a 95% yield of **2**. The ^1H and ^{13}C NMR spectra of synthetic **2** matched those of the natural product.[4] In this way, the stereoselective total synthesis of **2** was completed in eight steps, providing an overall yield of more than 5%.



Scheme 2. Synthesis of drimane **2**

From our experience of the effects of water on titanium(III) chemistry,[25,35,36] we deemed that the titanocene(III)-promoted reductive opening of epoxides **11a** and **11b** in aqueous media might be a convenient procedure for the synthesis of 3β-hydroxydihydroconfertifolin (**3**), a drimane lactone isolated from a fungus associated with aspen.[7]

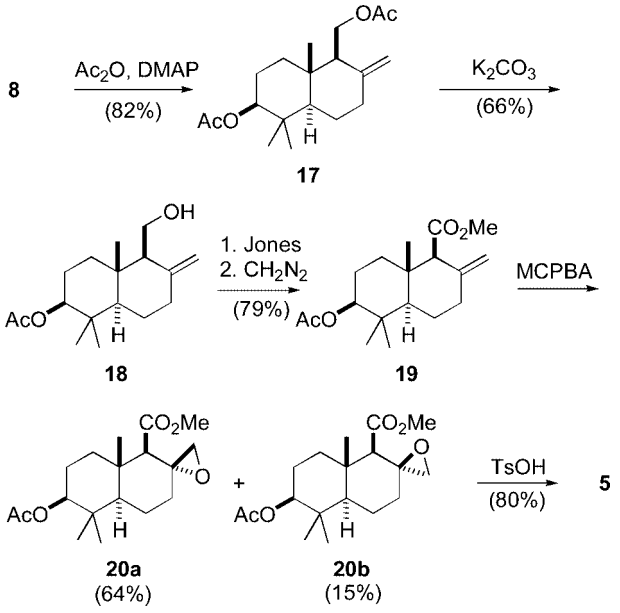
We thus started the synthesis of **3** by treating epoxides **11a** and **11b** with Cp_2TiCl_2/Mn in the presence of water (a in Scheme 3).[37] Under these conditions the reaction provided the reduced product **13** in an acceptable 65% yield (from the epimeric mixture), whereas the epimer at C-8 was not detected.[34] These results might be explained in terms of a C-8-centered tertiary radical, which would be formed equally from both epimers **11a** and **11b**. This radical is then trapped by a second titanocene(III) species at the less hindered face to give an alkyl-titanium(IV) complex. In anhydrous media this radical evolves towards the alkene **12**, presumably by elimination of $Cp_2Ti(Cl)H$.[36] In the presence of water, however, the alkyl-Ti^{IV} complex would undergo stereoselective protonolysis to give **13** as an unique stereoisomer. The two-step oxidation of **13** with Dess–Martin periodinane[38] and $NaClO_2$ gave the carboxylic acid **15**, which on basic treatment provided a 99% yield of the desired γ-lactone **3** (direct Jones oxidation of alcohol **13** to carboxylic acid **15**, however, gave a 1:1 mixture of epimers at C-8). In this way we achieved the first chemical synthesis of **3**, in ten steps and in an overall yield of more than 7%. The ^1H and ^{13}C NMR spectra of synthetic **3** matched those of natural 3β-hydroxydihydroconfertifolin,[7] confirming the structure proposed for the fungal metabolite.



Scheme 3. Synthesis of drimanes **3** and **4**

Both the (+) and the (–) enantiomers of 3β-hydroxycinnamolide (**4**) have been reported as natural products, the former from the plant *Warburgia stuhlmanii* [6] and the latter from the fungus *Peniophora polygonya*.[7] Their structures were established by spectroscopic methods,[6,7] and the absolute stereochemistry of the (–)-enantiomer (shown in **4**) was assigned on the basis of its CD spectrum.[7] We began the synthesis of **4** (b in Scheme 3) with a two-step oxidation of **12** via the conjugated aldehyde **16**. Subsequent oxidation of diester **16** and saponification provided the desired lactone **4** in a 69% yield. The first chemical synthesis of **4** was thus completed in ten steps and in 3% overall yield. The spectroscopic properties of synthetic **4** (except for the optical rotation) matched those of the natural product,[6,7] thus confirming the structure of 3β-hydroxycinnamolide.

3β-Acetoxydrimenin (**5**), found in the leaves of the tree *Drimys winteri*,[3] showed a β,γ′-unsaturated nonconjugated γ-lactone group integrated in the drimane skeleton, which was an interesting synthetic challenge. As epoxy esters have proven to be excellent precursors for the synthesis of lactones,[39,40] we decided to assay this strategy for the chemical preparation of **5** (see last step in Scheme 4).



Scheme 4. Synthesis of drimane **5**

We began the synthesis of **5** with the acetylation of the cornerstone intermediate **8** and subsequent selective saponification of the diacetate **17** to provide the primary alcohol **18**. Jones' oxidation of **18**, followed by treatment with diazomethane, provided ester **19**, which reacted with MCPBA to give oxiranes **20a** and **20b** (62% combined yield from **18**). Treatment of these epoxides with titanocene(III), however, only gave a discouraging 15% yield of the desired product **5**.[41] Fortunately, under acidic conditions the epimeric mixture of **20a** and **20b** evolved towards the endocyclic alkene **5**, providing a substantial yield of 80%. This result confirmed that the acid-induced cyclization of epoxy esters, previously reported by us for the formation of δ-lactones,[39] can also be used for the synthesis of γ-lactones. The IR, EIMS, and ^{1}H NMR spectra of synthetic **5** were in accordance with those reported for the metabolite isolated from *D. winteri*,[3] so the total synthesis of **5** was achieved in nine steps and in an overall yield of almost 6%.[42]

Evaluation of the Antifeedant Activity

The antifeedant effects of the 3-hydroxydrimanes **2–5** against several insect species with different feeding ecologies (*Spodoptera littoralis*, *Leptinotarsa decemlineata*, *Myzus persicae*, and *Ropalosiphon padi*) were tested, and the results are set out in Table 1. The drimane lactone 3β-hydroxydihydroconfertifolin (**3**) was the strongest antifeedant against *L. decemlineata*, followed by **5**, but effective antifeedant doses (EC_{50} values) could only be calculated for **3** (8.2 μg cm^{-2}, 3.7–18.1 lower-upper 95% confidence limits). The unsaturated lactone **4** had a moderate-to-strong effect on *M. persicae*, in contrast with the virtually inactive compound **3** (Table 1), possibly due to the presence of a Michael acceptor group in **4**. Finally, we observed no significant antifeedant or behavioral effect of compounds **2–5** either on *S. littoralis* or on *R. padi*.

Table 1. Antifeedant (%FI) effects of 3-hydroxydrimanes **2–5** on *S. littoralis* larvae and adult *L. decemlineata*; percent settling of apterous *M. persicae* and *R. padi* adults on control (%C) and treated (%T) leaf disks

	S. littoralis	*L. decemlineata*	*M. persicae*		*R. padi*	
	(%FI)[a]		%C	%T	%C	%T
2	20.0	12.1	52	48	37	63
3	48.7	83.5	59	41[b]	49	51
4	16.0	49.1	72	28[c]	52	48
5	38.8	66.5	47	53	47	53

[a] $FI = [1 - (T/C)]\times100$, where T and C are the consumption on control and treated leaf disks. [b] <0.05, [c] <0.00005. [d] <0.005, Mann Whitney W-Test (hypothesis: median $\%C >$ median $\%T$).

These compounds showed molecular and species-dependent selectivity, as previously shown for other drimanes.[13,14] Similar species selectivity has been reported for a *neo*-clerodane diterpene dialdehyde.[43]

Table 2 shows the performance parameters of orally injected *S. littoralis* larvae. A covariance analysis (ANCOVA1) of food consumption (ΔI) and biomass gains (ΔB) with initial larval weight as covariate (covariate $p > 0.05$) was performed to test for any significant effects of the sesquiterpenes on these variables.[43] Compounds **2** and **4** significantly decreased ΔI and ΔB (ANCOVA1 $p < 0.05$ for ΔB and ΔI). Treatment effects on ΔB disappeared with an additional covariance adjustment with ΔI as covariate, so we were able to conclude that these compounds had post-ingestive antifeedant effects with no further toxicity. Post-ingestive effects have been suggested previously for synthetic analogues (lactones) of polygodial and warbuganal

Table 2. Consumption (ΔI) and biomass gain (ΔB) of orally injected *Spodoptera littoralis* larvae and cytotoxic effects on Sf9 and CHO cells (* treatment p-level < 0.05, ANCOVA analysis with initial body weight as covariate)

	S. littoralis (% of control)		ED_{50} (μg ml^{-1})[a]	
	ΔI[b]	ΔB[c]	Sf9	CHO
2	51.3*	71.9*	>100	>100
3	92.9	106.7	>100	>100
4	65.3*	78.4*	>100	>100
5	98.7	106.5	34.35 (23.43, 50.36)[d]	>100

[a] D_{50} = Concentration needed to produce 50% cell viability. [b] I = mg food consumed (mg of dry weight). [c] B = change in insect body weight (mg of dry weight). [d] 95 % Confidence limits.

on *Pieris brassicae* and *L. decemlineata* larvae,[44] but no direct experimental evidence was provided.

Among the structurallyrelated drimanes tested, the least polar one, acetate **5,** showed moderate selective cytotoxicity against insect-derived Sf9 cells versus the mammalian CHO cell line, probably due to a combination of polarity and specific membrane factors. None of the other compounds affected the cell lines tested (Table 2).

Conclusions

In summary, we confirm the synthetic viability of the titanocene(III)-catalyzed cyclization of epoxypolyprenes for the chemical preparation of natural 3-hydroxydrimanes (**2**–**5**) with different functionalization patterns. We also tested the antifeedant properties of these drimanes against the insects *S. littoralis*, *L. decemlineata*, *M. persicae*, and *R. padi* and observed different activity levels. The antifeedant structure–activity variation of these compounds (lactones > alcohols) fits with the proposed mode of action for antifeedant drimanes by adduct formation with amino groups on the insect chemoreceptor.[45] We are currently trying to extend our synthetic strategy to the chemical preparation of more complex terpenoids. Additionally, as the asymmetric synthesis of (10*S*)-10,11-epoxyfarnesol has recently been described by Corey's group,[46] an enantioselective version of our method might presumably be developed without too much difficulty.

Experimental Section

General Remarks: In reactions employing titanocene, all solvents and additives were thoroughly deoxygenated prior to use. The numbering used in the NMR assignments corresponds to the drimane system and not the IUPAC nomenclature. The cornerstone intermediate **8** was prepared by our previously reported procedure.[25] The following known compounds were isolated as pure samples and showed NMR spectra identical to those reported: **2**,[4] **3**,[7] **4**,[6,7] and **5**.[3,42] Other general experimental details have been reported elsewhere.[29,36]

Diester 10: A mixture of **8** (190 mg, 0.68 mmol), benzoyl chloride (0.174 mL, 1.02 mmol), and DMAP (124 mg, 1.02 mmol) in pyridine (7 mL) was stirred at room temp. for 2 h. *t*BuOMe (15 mL) was then added and the mixture was washed with HCl (2 N), NaOH (2 N), and brine. The organic layer was dried (anhyd. Na_2SO_4), and the solvent was removed. The residue was subjected to flash chromatography (hexane/*t*BuOMe, 85:15), giving **10** (260 mg, quant): white solid; m.p. 105–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, J = 7.8 Hz, 2 H), 7.53 (t, J = 7.8 Hz, 1 H), 7.43 (t, J = 7.8 Hz, 2 H), 4.91 (br.s, 1 H), 4.81 (dd, J = 11.6, 4.3 Hz, 1 H), 4.57 (br.s, 1 H), 4.32 (dd, J = 11.3, 4.3 Hz, 1 H), 4.26 (dd, J = 11.3, 8.4 Hz, 1 H), 2.47 (ddd, J = 13.1, 3.8, 2.2 Hz, 1 H), 2.10–2.00 (m, 2 H), 2.06 (s, 3 H), 1.91 (dt, J = 12.5, 3.9 Hz, 1 H), 1.87–1.70 (m, 5 H), 1.56 (td, J = 12.9, 3.6 Hz, 1 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.82 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.43 (C), 166.30 (C), 146.11 (C), 132.89 (CH), 130.86 (C), 129.60 (CH), 128.54 (CH), 107.81 (CH_2), 81.06 (CH), 61.55 (CH_2), 54.50 (CH), 54.38 (CH), 38.66 (C), 38.49 (C), 37.36 (CH_2), 36.71 (CH_2), 28.49 (CH_3), 24.24 (CH_2), 23.40 (CH_2), 21.18 (CH_3), 16.95 (CH_3), 15.20 (CH_3). MS (70 eV, EI): *m*/*z* (%): 384 $[M]^+$ (1), 324 (15), 187 (40), 134 (100), 119 (37). HRMS (FAB): calcd. for $C_{24}H_{32}O_4Na$ 407.2198, found 407.2198.

Epoxides 11a and 11b: A sample of MCPBA (380 mg, 0.91 mmol) was added to a solution of **10** (317 mg, 0.82 mmol) in CH_2Cl_2 (50 mL) and the mixture was stirred at room temp. for 7.5 h. *t*BuOMe was then added, and the mixture was washed with NaOH (2 N) and brine. The organic layer was dried over anhyd. Na_2SO_4 and the solvent was removed. The residue was chromatographed (hexane/*t*BuOMe, 3:1) to afford **11b** (54 mg, 16%) and **11a** (230 mg, 70%). Data for **11b**: white solid; m.p. 135–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, J = 7.5 Hz, 2 H), 7.48 (t, J = 7.5 Hz, 1 H), 7.37 (t, J = 7.5 Hz, 2 H), 4.71 (dd, J = 11.5, 4.6 Hz, 1 H), 4.20 (br. d, J = 11.6 Hz, 1 H), 3.44 (dd, J = 11.6, 8.3 Hz, 1 H), 2.66 (d, J = 4.1 Hz, 1 H), 2.33 (d, J = 3 Hz, 1 H), 1.96 (s, 3 H), 1.94–1.60 (m, 7 H), 1.50–1.25 (m, 2 H), 1.15–1.05 (m, 1 H), 1.00 (s, 3 H), 0.92 (s, 3 H), 0.91 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.79 (C), 166.25 (C), 132.87 (CH), 130.86 (C), 129.59 (CH), 128.41 (CH), 80.96 (CH), 59.16 (CH_2), 56.38 (C), 54.06 (CH), 51.34 (CH), 49.59 (CH_2), 38.87 (C), 38.46 (C), 36.82 (CH_2), 35.41 (CH_2), 28.56 (CH_3), 23.64 (CH_2), 21.18 (CH_3), 19.65 (CH_2), 16.90 (CH_3), 15.48 (CH_3). MS (70 eV, EI): *m*/*z* (%): 400 $[M]^+$ (1), 218 (1), 203 (9), 105 (100). HRMS (FAB): calcd. for $C_{24}H_{32}O_5Na$ 423.2147, found 423.2147. Data for **11a**: white solid; m.p. 145–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, J = 7.5 Hz, 2 H), 7.46 (t, J = 7.5 Hz, 1 H), 7.35 (t, J = 7.5 Hz, 2 H), 4.68 (dd, J = 11.5, 4.5 Hz, 1 H), 3.85 (dd, J = 11.6, 6.0 Hz, 1 H), 3.69 (dd, J = 11.6, 3.0 Hz, 1 H), 2.50 (m, 2 H), 1.92 (s, 3 H), 1.90–1.10 (m, 10 H), 0.96 (s, 3 H), 0.88 (s, 3 H), 0.87 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.82 (C), 166.09 (C), 132.82 (CH), 130.68 (C), 129.47 (CH), 128.32 (CH), 80.82 (CH), 58.76 (CH_2), 57.22 (C), 53.91 (CH), 52.18 (CH), 51.30 (CH_2), 39.02 (C), 38.19 (C), 36.67 (CH_2), 35.51 (CH_2), 28.33 (CH_3), 23.51 (CH_2), 21.06 (CH_3), 19.41 (CH_2), 16.75 (CH_3), 15.23 (CH_3). MS (70 eV, EI): *m*/*z* (%): 400 $[M]^+$ (1), 310 (3), 218 (4), 105 (100). HRMS (FAB): calcd. for $C_{24}H_{32}O_5Na$ 423.2147, found 423.2157.

Allylic Alcohol 12: A mixture of Cp_2TiCl_2 (95 mg, 0.37 mmol) and Mn dust (55 mg, 1.00 mmol) in completely deoxygenated THF (25 mL) was stirred at room temp. until the red solution turned green. The solvent was then removed and anhydrous benzene (25 mL) was added. The green suspension of titanocene(III) was slowly added to an epimeric mixture of **11a** and **11b** (4:1 ratio, 48 mg, 0.12 mmol) in benzene (10 mL) and the reaction mixture was stirred at room temp. for 5 h. The reaction mixture was then quenched with 5% aqueous NaH_2PO_4 and extracted with *t*BuOMe. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. The residue was chromatographed (hexane/*t*BuOMe,1:1) to give **12** (18 mg, 38 %) as a vitreous solid: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, J = 7.5 Hz, 2 H), 7.57 (t, J = 7.5 Hz, 1 H), 7.45 (t, J = 7.5 Hz, 2 H), 5.85 (m, 1 H), 4.75 (dd, J = 11.4, 4.3, 1 H), 4.34 (dd, J = 11.7, 3.6 Hz, 1 H), 4.27–4.18 (m, 2 H), 3.98 (d, J = 12.8 Hz, 1 H), 2.20–2.15 (m, 1 H), 2.00–1.00 (m, 7 H), 2.05 (s, 3 H), 1.07 (s, 3 H), 0.93 (s, 3 H), 0.87 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.91 (C), 166.25 (C), 136.09 (C), 132.88 (CH), 130.75 (C), 129.55 (CH), 128.39 (CH), 126.05 (CH), 81.14 (CH), 65.86 (CH_2), 62.91 (CH_2), 50.42 (CH), 49.27 (CH), 37.97 (C), 37.20 (CH_2), 35.56 (C), 28.10 (CH_3), 23.86 (CH_2), 22.97 (CH_2), 21.21 (CH_3), 16.79 (CH_3), 14.57 (CH_3). MS (70 eV, EI): *m*/*z* (%): 340 (7), 173 (10), 105 (100). HRMS (FAB): calcd. for $C_{24}H_{32}O_5Na$ 423.2147, found 423.2144.

Drimane 2: Compound **12** (10 mg, 0.025 mmol) in ethanolic KOH (0.5 M, 4 mL) was stirred at room temp. for 7 h. *t*BuOMe was then

added, and the mixture was washed with HCl (2 N) and brine The organic layer was dried over anhyd. Na_2SO_4, and the solvent was removed. Flash chromatography of the residue (*t*BuOMe) gave **2** (6 mg, 95 %).

Alcohol 13: A mixture of Cp_2TiCl_2 (360 mg, 1.41 mmol) and Mn dust (206 mg, 3.76 mmol) in THF (35 mL) was stirred at room temp. until the red solution turned green, and then a completely deoxygenated mixture of H_2O (0.25 mL) and THF (25 mL) was added. The deep blue suspension obtained was slowly added to **11** (188 mg, 0.47 mmol) in THF (10 mL), and the system was stirred at room temp. for 5.5 h. The reaction mixture was then quenched with aqueous NaH_2PO_4 (5%) and extracted with *t*BuOMe. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. Flash chromatography of the residue (hexane/*t*BuOMe, 3:7) gave **13** (120 mg, 65%): white solid; m.p. 100–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, J = 7.5 Hz, 2 H), 7.48 (t, J = 7.5 Hz, 1 H), 7.37 (t, J = 7.5 Hz, 2 H), 4.65 (dd, J = 11.5, 4.8 Hz, 1 H), 4.16 (dd, J = 11.3, 5.4 Hz, 1 H), 4.06 (dd, J = 11.3, 8.5 Hz, 1 H), 3.61 (dd, J = 10.4, 2.9 Hz, 1 H), 3.53 (t, J = 10.4, 1 H), 1.98 (s, 3 H), 1.75–1.00 (m, 11 H), 0.97 (s, 3 H), 0.87 (s, 3 H), 0.83 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.51 (C), 166.25 (C), 132.83 (CH), 130.79 (C), 129.53 (CH), 128.36 (CH), 81.00 (CH), 62.94 (CH_2), 61.67 (CH_2), 55.41 (CH), 51.68 (CH), 39.26 (CH), 38.23 (C), 37.23 (CH_2), 36.88 (C), 28.67 (CH_2), 28.22 (CH_3), 23.58 (CH_2), 21.11 (CH_3), 17.33 (CH_2), 16.76 (CH_3), 16.40 (CH_3). MS (70 eV, EI): *m*/*z* (%): 220 (10), 165 (10), 105 (100). HRMS (FAB): calcd. for $C_{24}H_{34}O_5Na$ 425.2303, found 425.2306.

Aldehyde 14: Dess–Martin periodinane (172 mg, 0.32 mmol) and $NaHCO_3$ (30 mg, 0.32 mmol) were added to a solution of **13** (64 mg, 0.16 mmol) in CH_2Cl_2 (15 mL), and the mixture was stirred at room temp. for 38 h. *t*BuOMe was then added, and the solution was washed with a mixture of aqueous $Na_2S_2O_3$ (10%) and saturated $NaHCO_3$ (1:1) and with brine. The organic layer was dried (anhyd Na_2SO_4) and the solvent was removed. The residue was chromatographed (hexane/*t*BuOMe, 55:45) to give **14** (54 mg, 85%): white solid; m.p. 154–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.96 (s, 1 H), 8.05 (d, J = 7.5 Hz, 2 H), 7.57 (t, J = 7.5 Hz, 1 H), 7.45 (t, J = 7.5 Hz, 2 H), 4.75 (dd, J = 11.6, 4.4 Hz, 1 H), 4.50–4.40 (m, 2 H), 2.68 (br. t, J = 5 Hz, 1 H), 2.48 (br. d, J = 12.7 Hz, 1 H), 2.10 (s, 3 H), 2.05–1.00 (m, 9 H), 0.96 (s, 3 H), 0.88 (s, 3 H), 0.82 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.76 (C), 171.06 (C), 166.23 (C), 132.92 (CH), 130.72 (C), 129.56 (CH), 128.41 (CH), 80.74 (CH), 61.89 (CH_2), 54.78 (CH), 51.80 (CH), 47.08 (CH), 38.21 (C), 37.41 (C), 36.66 (CH_2), 28.31 (CH_3), 25.63 (CH_2), 23.63 (CH_2), 21.08 (CH_3), 18.52 (CH_2), 16.76 (CH_3), 15.74 (CH_3). MS (70 eV, EI): *m*/*z* (%): 340 (1), 250 (5), 190 (16), 105 (100), 77 (20). HRMS (FAB): calcd. for $C_{24}H_{32}O_5Na$ 423.2147, found 423. 2151.

Carboxylic Acid 15: A mixture of $NaClO_2$ (220 mg, 1.4 mmol) and $NaH_2PO_4{\cdot}H_2O$ (163 mg, 1.05 mmol) was added to a solution of **14** (70 mg, 0.17 mmol) in a mixture of *t*BuOH/H_2O/2-methyl-2-butene (4.5:1.6:1 ratio, 17 mL). The solution was stirred at room temp. for 7 h and was then extracted with *t*BuOMe. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. The residue was chromatographed (hexane/*t*BuOMe, 3:2) to give **15** (55 mg, 75%): white solid; m.p. 162–163 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, J = 7.5 Hz, 2 H), 7.57 (t, J = 7.5 Hz, 1 H), 7.45 (t, J = 7.5 Hz, 2 H), 4.74 (dd, J = 11.2, 4.5 Hz, 1 H), 4.47 (dd, J = 11.4, 8.0 Hz, 1 H), 4.34 (dd, J = 11.4, 5.7 Hz, 1 H), 2.89 (t, J = 4.2 Hz, 1 H), 2.36 (br. d, J = 12.1 Hz, 1 H), 2.07 (s, 3 H), 1.85–1.25 (m, 9 H), 1.03 (s, 3 H), 0.96 (s, 3 H), 0.95 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.56 (C), 171.28 (C), 166.33 (C), 132.91 (CH), 130.80 (C), 129.62 (CH), 128.44 (CH), 81.01 (CH), 63.64 (CH_2), 55.35 (CH), 51.89 (CH), 39.18 (CH), 38.32 (C), 37.88 (C), 36.89 (CH_2), 28.49 (CH_2), 28.34 (CH_3), 23.65 (CH_2), 21.20 (CH_3), 18.72 (CH_2), 16.81 (CH_3), 14.77 (CH_3). MS (70 eV, EI): *m*/*z* (%): 281 (7), 234 (30), 207, 191 (27), 105 (100). HRMS (FAB): calcd. for $C_{24}H_{32}O_6Na$ 439.2096, found 439. 2101.

3β-Hydroxydihydroconfertifolin (3): A sample of **15** (30 mg, 0.07 mmol) in ethanolic KOH (0.5 M, 20 mL) was stirred at room temp. for 4 h. *t*BuOMe was then added and the mixture was washed with HCl (2 N) and brine. The organic layer was dried (anhyd Na_2SO_4), and the solvent was removed. Flash chromatography (*t*BuOMe) of the residue gave **3** (18 mg, 99%).

Conjugated Aldehyde 16: A mixture of **12** (80 mg, 0.2 mmol) and MnO_2 (500 mg, 5.7 mmol) in CH_2Cl_2 (15 mL) was stirred at room temp. for 2 h. The mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite®, and the solvent was removed from the filtrate. The residue was chromatographed (hexane/*t*BuOMe, 4:1) to give **16** (50 mg, 63%): vitreous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.44 (s, 1 H), 8.03 (d, J = 7.2 Hz, 2 H), 7.56 (t, J = 7.2 Hz, 1 H), 7.44 (t, J = 7.2 Hz, 2 H), 6.93 (m, 1 H), 4.76 (dd, J = 11.5, 4.4 Hz, 1 H), 4.62 (dd, J = 11.7, 5.7 Hz, 1 H), 4.45 (br. d, J = 11.7 Hz, 1 H), 2.50–2.40 (m, 2 H), 2.10–1.00 (m, 6 H), 1.95 (s, 3 H), 1.15 (s, 3 H), 0.98 (s, 3 H), 0.90 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.81 (CH), 170.80 (C), 166.22 (C), 152.26 (CH), 140.07 (C), 133.01 (CH), 130.69 (C), 129.62 (CH), 128.58 (CH), 80.85 (CH), 59.99 (CH_2), 48.84 (CH), 48.46 (CH), 37.94 (C), 37.41 (CH_2), 35.83 (C), 28.25 (CH_3), 24.46 (CH_2), 23.72 (CH_2), 21.10 (CH_3), 16.98 (CH_3), 14.76 (CH_3). MS (70 eV, EI): *m*/*z* (%): 338 (4), 216 (8), 159 (10), 105 (100). HRMS (FAB): calcd. for $C_{24}H_{30}O_5Na$ 421.1991, found 421.1994.

3β-Hydroxycinnamolide (4): A solution of $NaClO_2$ (189 mg, 1.2 mmol) and $NaH_2PO_4{\cdot}H_2O$ (141 mg, 0.9 mmol) in water (5 mL) was slowly added to a mixture of **16** (60 mg, 0.15 mmol) and 2-methyl-2-butene (2 mL) in *t*BuOH(10 mL). The reaction mixture was stirred at room temp. for 5 h, and the solvent was then removed. The obtained mixture was extracted with *t*BuOMe, the ethereal solution was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. The residue was dissolved in methanolic KOH (2 M, 5 mL) and stirred at room temp. for 2 h. *t*BuOMe was then added and the mixture was washed with HCl (2 N) and brine. The organic layer was dried (anhyd Na_2SO_4), and the solvent was removed. Flash chromatography (hexane/*t*BuOMe, 3:2) of the residue gave **4** (26 mg, 69%).

Diacetate 17: A mixture of **8** (120 mg, 0.43 mmol), Ac_2O (0.05 mL, 0.64 mmol), and DMAP (80 mg, 0.64 mmol) in CH_2Cl_2 (10 mL) was stirred at room temp. for 1 h. The mixture was then diluted with *t*BuOMe and washed with HCl (2 N), saturated $NaHCO_3$, and brine. The organic layer was dried over anhyd Na_2SO_4, and the solvent was removed. Flash chromatography (hexane/*t*BuOMe, 85:15) of the residue gave **17** (113 mg, 82%): white solid; m.p. 80–82 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.83 (br.s, 1 H), 4.48 (br.s, 1 H), 4.49 (dd, J = 10.2, 4.05 Hz, 1 H), 4.24 (dd, J = 11.3, 4.5 Hz, 1 H), 4.16 (dd, J = 11.3, 8.2 Hz, 1 H), 2.38 (ddd, J = 13.1, 3.9, 2.4 Hz, 1 H), 2.00–1.00 (m, 9 H), 2.01 (s, 3 H), 1.98 m(s, 3 H), 0.84 (s, 3 H), 0.82 (s, 3 H), 0.74 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.25 (C), 170.92 (C), 146.09 (C), 107.73 (CH_2), 80.42 (CH), 61.48 (CH_2), 54.42 (CH), 54.38 (CH), 38.59 (C), 38.06 (C), 37.33 (CH_2), 36.68 (CH_2), 28.30 (CH_3), 24.15 (CH_2), 23.36 (CH_2), 21.30 (CH_3), 21.12 (CH_3), 16.63 (CH_3), 15.15 (CH_3). MS (70 eV, EI): *m*/*z* (%): 262 (10), 202 (40), 187 (40), 135 (100). HRMS (FAB): calcd. for $C_{19}H_{30}O_4Na$ 345.2041, found 345.2046.

Alcohol 18: A sample of diacetate **17** (110 mg, 0.34 mmol) was dissolved in methanolic K_2CO_3 (0.5 M, 20 mL) at 0 °C and stirred for 2 h. The mixture was then diluted with *t*BuOMe and washed with HCl (2 N) and brine. The organic layer was dried (anhyd Na_2SO_4), and the solvent was removed. Flash chromatography (hexane/*t*BuOMe, 1:1) of the residue provided alcohol **18** (48 mg, 50%) and starting diacetate **17** (42 mg, 38%). The recovered starting material was treated under the same conditions, thus increasing the overall yield of **18** to 66%. Data for **18**: white solid; m.p. 105–107 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.93 (br.s, 1 H), 4.65 (br.s, 1 H), 4.51 (dd, J = 11.5, 4.3 Hz, 1 H), 3.82–3.71 (m, 2 H), 2.42 (ddd, J = 12.9, 4.0, 2.5 Hz, 1 H), 2.00–1.00 (m, 9 H), 2.02 (s, 3 H), 0.85 (s, 3 H), 0.82 (s, 3 H), 0.73 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.95 (C), 147.06 (C), 106.98 (CH_2), 80.51 (CH), 58.80 (CH), 58.76 (CH_2), 54.51 (CH), 38.57 (C), 38.08 (C), 37.60 (CH_2), 36.69 (CH_2), 28.31 (CH_3), 24.23 (CH_2), 23.64 (CH_2), 21.30 (CH_3), 16.65 (CH_3), 15.37 (CH_3). MS (70 eV, EI): *m*/*z* (%): 280 $[M]^+$ (1), 262 (6), 220 (20), 135 (100). HRMS (FAB): calcd. for $C_{17}H_{28}O_3Na$ 303.1936, found 303.1940.

Methyl Ester 19: A sample of Jones' reagent (0.2 mL) was added to a solution of **18** (60 mg, 0.22 mmol) in acetone (10 mL), and the system was stirred at room temp. for 3 h. The solvent was then removed, and the residue was dissolved in *t*BuOMe, washed with brine, dried over anhyd Na_2SO_4, and concentrated. The residue was stirred with a saturated solution of CH_2N_2 in Et_2O (5 mL) for 30 min. The solvent was removed and the residue was subjected to flash chromatography (hexane/*t*BuOMe, 85:15) to give **19** (52 mg, 79%): white solid; m.p. 125–127 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.83 (s, 1 H), 4.65 (s, 1 H), 4.50 (dd, J = 10.5, 5.4 Hz, 1 H), 3.62 (s, 3 H), 2.74 (s, 1 H), 2.41 (ddd, J = 13.5, 4.5, 2.2 Hz, 1 H), 2.10–1.95 (m, 1 H), 2.02 (s, 3 H), 1.80–1.00 (m, 7 H), 1.07 (s, 3 H), 0.86 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.81 (C), 165.59 (C), 143.12 (C), 108.96 (CH_2), 80.51 (CH), 62.53 (CH), 53.88 (CH), 51.04 (CH_3), 38.81 (C), 38.03 (C), 36.54 (CH_2), 35.84 (CH_2), 28.23 (CH_3), 23.97 (CH_2), 22.77 (CH_2), 21.29 (CH_3), 16.62 (CH_3), 14.27 (CH_3). MS (70 eV, EI): *m*/*z* (%): 173 (8), 135 (100). HRMS (FAB): calcd. for $C_{18}H_{28}O_4Na$ 331.1885, found 331.1889.

Epoxides 20a and 20b: A sample of MCPBA (140 mg, 0.05 mmol) was added to a solution of **19** (52 mg, 0.17 mmol) in CH_2Cl_2 (8 mL), and the system was stirred at room temp. for 6 h. The mixture was then diluted with *t*BuOMe and washed with NaOH (2 N) and brine. The organic layer was dried (anhyd Na_2SO_4), and the solvent was removed. Flash chromatography (hexane/MeO*t*Bu 3:1) of the residue afforded **20a** (35 mg, 64%) and **20b** (8 mg, 15%). Data for **20a**: white solid; m.p. 115–116 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.51 (dd, J = 10.5, 4.9 Hz, 1 H), 3.57 (s, 3 H), 3.33 (dd, J = 4.9, 1.5 Hz, 1 H), 2.62 (s, 1 H), 2.57 (d, J = 4.9 Hz, 1 H), 2.03 (s, 3 H), 2.00–1.00 (m, 9 H), 1.16 (s, 3 H), 0.89 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.84 (C), 170.73 (C), 80.25 (CH), 59.68 (CH), 56.81 (C), 53.57 (CH), 53.05 (CH_2), 51.26 (CH_3), 39.63 (C), 37.96 (C), 36.63 (CH_2), 34.95 (CH_2), 28.33 (CH_3), 23.53 (CH_2), 21.28 (CH_3), 21.17 (CH_2), 16.60 (CH_3), 14.54 (CH_3). HRMS (FAB): calcd. for $C_{18}H_{28}O_5Na$ 347.1834, found 347.1825. Data for **20b**: white solid; m.p. 111–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.51 (dd, J = 9.0, 6.8 Hz, 1 H), 3.60 (s, 3 H), 2.59 (s, 1 H), 2.43 (d, J = 4.1 Hz, 1 H), 2.39 (d, J = 4.1 Hz, 1 H), 2.04 (s, 3 H), 2.00–1.00 (m, 9 H), 1.38 (s, 3 H), 0.93 (s, 3 H), 0.89 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.94 (C), 169.80 (C), 80.44 (CH), 58.16 (CH), 56.22 (C), 53.74 (CH), 51.14 (CH_3), 49.15 (CH_2), 38.90 (C), 38.03 (C), 36.89 (CH_2), 34.70 (CH_2), 28.33 (CH_3), 23.43 (CH_2), 21.31 (CH_3), 19.63 (CH_2), 16.65 (CH_3), 14.54 (CH_3). HRMS (FAB): calcd. for $C_{18}H_{28}O_5Na$ 347.1834, found 347.1832.

3β-Acetoxydrimenin (5): A mixture of epoxides **20** (35 mg, 0.11 mmol) and $TsOH\cdot H_2O$ (20 mg, 0.16 mmol) in $CHCl_3$ (10 mL) was heated under reflux for 2 h. The mixture was then diluted with CH_2Cl_2 and washed with brine. The organic layer was dried (anhyd Na_2SO_4), and the solvent was removed. Flash chromatography (hexane/*t*BuOMe, 7:3) of the residue gave **5** (25 mg, 80%).

Bioassays: Insect rearing, choice feeding assays, and oral cannulations were conducted as described by Reina et al.[47] Cytotoxicity on Sf9 and CHO cell lines were conducted by described procedures.[48]

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[1] For a classical overview on drimane sesquiterpenoids and other terpenoids found in nature see: J. D. Connolly, R. A. Hill, *Dictionary of Terpenoids*; Chapman and Hall: London, **1991.**
[2] M. de Bernardi, G. Mellerio, G. Vidari, P. Vita-Finzi, G. Fronza, *J. Chem. Soc. Perkin Trans. 1* **1980**, 221–226.
[3] J. R. Sierra, J. T. López, M. J. Cortés, *Phytochemistry* **1986**, *25*, 253–254.
[4] W. A. Ayer, P. A. Craw, *Can. J. Chem.* **1989**, *67*, 1371–1380.
[5] M. S. Al-Said, S. M. El-Khawaja, F. S. El-Feraly, C. D. Hufford, *Phytochemistry* **1990**, *29*, 975–977.
[6] D. Kioy, A. I. Gray, P. G. Waterman, *Phytochemistry* **1990**, *29*, 3535–3538.
[7] W. A. Ayer, L. S. Trifonov, *J. Nat. Prod.* **1992**, *55*, 1454–1461.
[8] U. Jacobsson, A. K. Muddathir, *Phytochemistry* **1992**, *31*, 4207–4211.
[9] H. Takahashi, M. Toyota, Y. Asakawa, *Phytochemistry* **1993**, *33*, 1055–1059.
[10] B. P. Ying, G. Peiser, Y. Y. Ji, K. Mathias, D. Tutko, Y. S. Hwang, *Phytochemistry* **1995**, *38*, 909–915.
[11] W. F. Fleck, B. Schlegel, P. Hoffmann, M. Ritzau, S. Heinze, U. Grafe, *J. Nat. Prod.* **1996**, *59*, 780–781.
[12] I. Sakio, Y. J. Hirano, M. Hayashi, K. Komiyama, M. Ishibashi, *J. Nat. Prod.* **2001**, *64*, 726–731.
[13] G. Powell, J. Hardie, J. A. Pickett, *Entomol. Exp. Appl.* **1997**, *84*, 189–193.
[14] L. Messchendorp, G. J. Z. Gols, J. J. A. van Loon, *J. Chem. Ecol.* **1998**, *24*, 1433–1446.
[15] B. J. M. Jansen, A. de Groot, *Nat. Prod. Rep.* **1991**, *8*, 309–318.
[16] K. A. Parker, L. Resnick, *J. Org. Chem.* **1995**, *60*, 5726–5728.
[17] K. Takao, T. Sasaki, T. Kozaki, Y. Yanagisawa, K. Tadano, A. Kawashima, H. Shinonaga, *Org. Lett.* **2001**, *3*, 4291–4294.
[18] J. R. Falck, K. K. Reddy, S. Chandrasekhar, *Tetrahedron Lett.* **1997**, *38*, 5245–5248.
[19] S. Manna, P. Yadagiri, J. R. Falck, *J. Chem. Soc. Chem. Commun.* **1987**, 1324–1325.
[20] K. Mori, H. Watanabe, *Tetrahedron* **1986**, *42*, 273–281.
[21] T. Tozyo, F. Yasuda, H. Nakai, H. Tada, *J. Chem. Soc. Perkin Trans. 1* **1992**, 1859–1866.
[22] G. Aranda, M. Cortés, M. Maurs, R. Azerad, *Tetrahedron: Asymmetry* **2001**, *12*, 2013–2018 and references cited therein.
[23] U. Hoffmann, Y. Gao, B. Pandey, S. Klinge, K.-D. Warzecha, C. Krüger, H. D. Roth, M. Demuth, *J. Am. Chem. Soc.* **1993**, *115*, 10358–10359.

[24] G. Vidari, S. Beszant, J. El Merabet, M. Bovolenta, G. Zanoni, *Tetrahedron Lett.* **2002**, *43*, 2687–2690 and references cited therein.
[25] J. Justicia, A. Rosales, E. Buñuel, J. L. Oller-López, M. Valdivia, A. Haïdour, J. E. Oltra, A. F. Barrero, D. J. Cárdenas, J. M. Cuerva, *Chem. Eur. J.* **2004**, *10*, 1778–1788.
[26] For pioneering works in this field see: T. V. Rajan Babu, W. A. Nugent, *J. Am. Chem. Soc.* **1994**, *116*, 986–997.
[27] For the first catalytic version see: A. Gansäuer, H. Bluhm, M. Pierobon, *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859.
[28] Epoxide **7** was obtained by treatment of *all-trans*-farnesyl acetate with aqueous NBS and subsequently with base. It is worth noting that the acid-induced cyclization of **7** gave a complex mixture from which the endocyclic regioisomer **9** could be isolated at modest yield but no formation of the exocyclic alkene **8** was detected. See: E. E. van Tamelen, A. Storni, E. J. Hessler, M. Schwartz, *J. Am. Chem. Soc.* **1963**, *85*, 3295–3296.
[29] A. F. Barrero, J. M. Cuerva, M. M. Herrador, M. V. Valdivia, *J. Org. Chem.* **2001**, *66*, 4074–4078.
[30] D. M. Hollinshead, S. C. Howell, S. V. Ley, M. Mahon, N. M. Ratcliffe, P. A. Worthington, *J. Chem. Soc. Perkin Trans. 1* **1983**, 1579–1589.
[31] For experimental details see Supporting Information (see footnote on the first page of this article).
[32] Similar results have recently been observed during the synthesis of 9-fluorodrimanes, see: A. Abad, C. Agulló, A. C. Cuñat, D. Pardo, *Tetrahedron Lett.* **2003**, *44*, 1899–1902.
[33] Besides allylic alcohol **12**, a mixture of saturated and unsaturated aldehydes together with carboxylic acids was obtained. For a precedent involving the formation of saturated aldehydes, see: K. V. Bhaskar, L. N. Mander, *Tetrahedron Lett.* **1996**, *37*, 719–722.
[34] The reaction was repeated with pure samples of **11a** and **11b**, similar results being obtained in both cases except for the longer reaction time required for **11b**.
[35] A. F. Barrero, A. Rosales, J. M. Cuerva, J. E. Oltra, *Org. Lett.* **2003**, *5*, 1935–1938.
[36] A. F. Barrero, J. E. Oltra, J. M. Cuerva, A. Rosales, *J. Org. Chem.* **2002**, *67*, 2566–2571.
[37] It is believed that the blue species generated in situ by stirring Cp_2TiCl_2 and Mn dust in THF/H_2O has the structure $[Cp_2Ti^{III}(H_2O)]^+Cl^-$, see: M. C. Barden, J. Schwartz, *J. Am. Chem. Soc.* **1996**, *118*, 5484–5485.
[38] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
[39] A. F. Barrero, J. E. Oltra, M. Álvarez, A. Rosales, *J. Org. Chem.* **2002**, *67*, 5461–5469.
[40] M. Liapis, V. Ragoussis, N. Ragoussis, *J. Chem. Soc. Perkin Trans. 1* **1985**, 815–817.
[41] Besides lactone **5**, a mixture of aldehydes, unsaturated aldehydes and non-lactonized allylic alcohols were obtained.
[42] A previously reported synthesis, using carvone as starting material, required 13 steps and provided an overall yield of 4%: H. J. Swarts, H. A. A. Verstegen-Haaksma, B. J. M. Jansen, A. de Groot, *Tetrahedron* **1994**, *50*, 10083–10094.
[43] A. González-Coloma, C. Gutiérrez, J. M. Del Corral, M. Gordaliza, M. L. de la Puente, A. San Feliciano, *J. Agric. Food Chem.* **2000**, *48*, 3677–3681.
[44] L. Messchendorp, G. J. Z. Gols, J. J. van Loon, *Entomol. Exp. Appl.* **2000**, *95*, 217–227.
[45] B. J. M. Jansen, A. de Groot, *Nat. Prod. Rep.* **1991**, *8*, 309–318.
[46] A. X. Huang, Z. M. Xiong, E. J. Corey, *J. Am. Chem. Soc.* **1999**, *121*, 9999–10003.
[47] M. Reina, A. González-Coloma, C. Gutiérrez, R. Cabrera, M. L. Rodríguez, V. Fajardo, L. Villarroel, *J. Nat. Prod.* **2001**, *64*, 6–11, and references therein.
[48] A. González-Coloma, A. Guadaño, C. De Inés, R. Martinez-Díaz, D. Cortes, *Z. Naturforsch. Teil C* **2002**, *57*, 1028–1034.
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