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Asymmetric Synthesis of 1,2-Dioxolane-3-acetic Acids: Synthesis and Configurational Assignment of Plakinic Acid A

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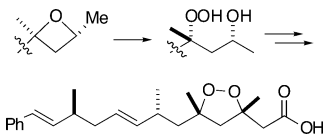
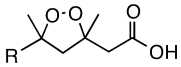


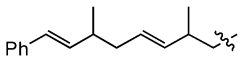
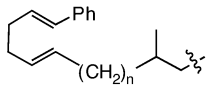
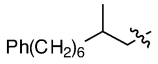
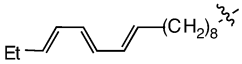
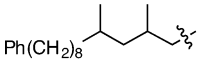
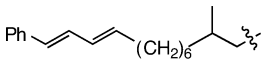
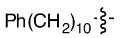
The first asymmetric synthesis of 1,2-dioxolane-3-acetic acids is reported. Key features include the stereoselective opening of enantiomerically enriched oxetanes by hydrogen peroxide, conversion of the resulting 4-hydroperoxy-2-alkanols to 3-alkoxy-1,2-dioxolanes, and Lewis acid mediated homologation of the latter with a thioester silyl ketene acetal. The approach is modeled on 3,5-dimethyl-5-hexadecyl-1,2-dioxolane-3-acetic acid (**1a**), an unnamed natural product, and an optimized strategy is applied to the synthesis of four stereoisomers of plakinic acid A (**2**), allowing a configurational assignment of this incompletely characterized natural product.

Introduction

The plakinic acids are a large family of marine natural products that have been reported to display cytotoxicity against fungal and cancer cell lines (Chart 1).[1−9] The absolute stereochemistry has not been established for any member of the family and no asymmetric synthesis of a plakinic acid has yet been reported. A racemic synthesis of **1b** has been reported based upon sequential inter- and intramolecular peroxymercurations of a dienoate.[10] This approach, while unquestionably efficient, is neither stereoselective nor compatible with the side chain unsaturation present in many members of the family. We recently reported a racemic approach to substituted dioxolanes, including **1a**, via Lewis acid mediated reactions of alkoxydiox-

CHART 1. Plakinic Acids and Related Compounds



R		Plakinate	Reference
$C_{16}H_{33}$ **1a**	$C_{15}H_{31}$ **1b**	(unnamed)	1
	**2**	A (3,5-cis)	2
	n = 4	C (3,5-cis); *epi*- C (3,5-trans)	3
	n = 2	D (3,5-cis) *epi*- D (3,5-trans)	3
		*epi*-E (3,5-trans)	4
		F (3,5-cis) *epi*-F (3,5-trans)	5
		G (3,5-cis) *epi*-G (3,5-trans)	6
		unnamed (3,5-cis) unnamed (3,5,trans)	7
		andavadoic acid (3,5,trans)	8

(1) Patil, A. D. PCT Int. Appl. WO 8704708, 2987; *Chem. Abstr.* **1988**, *109*, 17027f.
(2) Phillipson, D. W.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 7735−7736.
(3) Davidson, B. S. *J. Org. Chem.* **1991**, *56*, 6722−6724.
(4) Horton, P. A.; Longley, R. E.; Kelly-Borges, M.; McConnell, O. J.; Ballas, L. M. *J. Nat. Prod.* **1994**, *57*, 1374−1381.
(5) Chen, Y.; Killday, K. B.; McCarthy, P. J.; Schimoler, R.; Chilson, K.; Selitrennikoff, C.; Pomponi, S. A.; Wright, A. E. *J. Nat. Prod.* **2001**, *64*, 262−264.
(6) Sandler, J. S.; Colin, P. L.; Hooper, J. N. A.; Faulkner, D. J. *J. Nat. Prod.* **2002**, *65*, 1258−1261. This paper describes "epiplakinic acid H", which might be better described as plakinic acid G.
(7) Chen, Y.; McCarthy, P. J.; Harmody, D. K.; Schimoler-O'Rourke, R.; Chilson, K.; Selitrennikoff, C.; Pomponi, S.; Wright, A. E. *J. Nat. Prod.* **2002**, *65*, 1509−1512.
(8) Rudi, A.; Afanil, R.; Gravalos, L, G.; Aknin, M.; Gaydou, E.; Vacelet, J.; Kashman, Y. *J. Nat. Prod.* **2003**, *66*, 682−685.
(9) For reviews of peroxide natural products, see: Casteel, D. A. *Nat. Prod. Rep.* **1999**, *16*, 55−73; **1992**, *9*, 289−311.
(10) Bloodworth, A. J.; Bothwell, B. D.; Collins, A. N.; Maidwell, N. L. *Tetrahedron Lett.* **1996**, *37*, 1885−1888.

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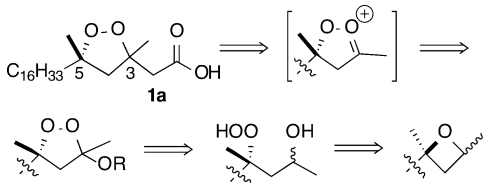
SCHEME 1. Retrosynthetic Approach to 1a



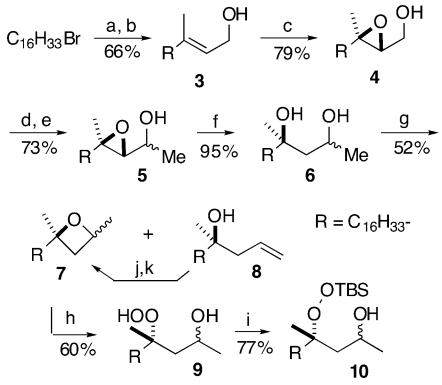
olanes with electron-rich alkenes.[11] However, the utility of this methodology was limited by the absence of methods for asymmetric synthesis of alkoxydioxanes. We recently reported a new method for synthesis of 1,3-peroxyalkanols that appeared to offer a route to enantiomerically enriched alkoxydioxanes and therefore dioxolane acetic acids.[12] We now describe the asymmetric synthesis of dioxolane **1a** as well as four candidate structures for plakinic acid A (**2**).[13]

Results and Discussion

As an initial target on which to model our approach, we chose **1a**, in which stereochemical issues are limited to the substitution on the dioxolane ring (Scheme 1). As in the racemic studies, introduction of the 1,2-dioxolane-3-acetic acid would be achieved through reaction of a thioester silyl ketene acetal with an alkoxydioxolane,[11] a reaction that proceeds via an intermediate peroxycarbenium ion. However, in contrast to the earlier work, the 1,2-dioxolane would be derived from an enantiomerically enriched 2,4-hydroperoxyalkanol prepared through opening of a tertiary oxetane by hydrogen peroxide.[12] Enantiomerically enriched oxetanes are available from 2,3-epoxy alcohols, making it possible to select the absolute stereochemistry of the dioxolane acetic acid through the choice of asymmetric epoxidation catalyst.

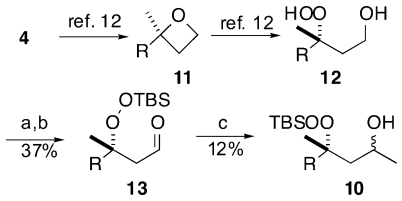
The synthesis began with allyl alcohol **3**, derived from carbalumination of octadecyne, (Scheme 2). Asymmetric epoxidation under stoichiometric conditions and in the presence of pentane as a nonpolar additive[14] provided the 2,3-epoxyalcohol **4** in 84% enantiomeric excess.[15] The derived aldehyde underwent addition of MeMgBr to furnish a 3:1 mixture of epimeric epoxy alcohols (**5**). As the hydroxyl-bearing stereocenter would be eventually destroyed, we elected to carry on the mixture of epimers. Red-Al reduction of the epoxy alcohols provided an excellent yield of 2,4-diols (**6**),[16] which were subjected to one-pot tosylation/cyclization to form a mixture of epimeric oxetanes.[12,17,18] The oxetanes were accompanied by a small amount of an elimination byproduct (**8**), which could

SCHEME 2. Synthesis of 4-Hydroperoxy-2-alkanol[a]



[a] Reagents and conditions: (a) LiCCH, ethylenediamine; (b) Cp_2ZrCl_2, $AlMe_3$, *n*-BuLi, $(CH_2O)_n$; (c) Ti(O*i*Pr)$_4$, (−)-DET, **3**, *t*-BuOOH, CH_2Cl_2/pentane; (d) Dess−Martin periodinane; (e) MeMgBr; (f) Red-Al; (g) *t*-BuOK, TsCl, *t*-BuOK, THF; (h) ethereal H_2O_2, Yb(OTf)$_3$; (i) LiHMDS, TBSCl; (j) NIS; (k) *n*-Bu_3SnH, AIBN.

SCHEME 3 [a]



[a] Reagents and conditions: (a) LiHMDS, TBSCl; (b) Dess−Martin periodinane; (c) Me_3Al.

be recycled to oxetane via iodoetherification and reductive dehalogenation.[19] Yb(OTf)$_3$-catalyzed opening of oxetane **7** with ethereal H_2O_2 proceeded smoothly to provide 4-hydroperoxy-2-alkanol **9**.[12] Selective protection of the hydroperoxide group with a lithium amide and TBSCl cleanly furnished peroxyalkanol **10**.

We briefly explored an alternate approach to peroxyalkanol **10** based upon homologation of a 3-peroxyalkanal (Scheme 3). Hydroperoxyalkanol **12** was prepared via acid-catalyzed opening of 2,2-disubstituted oxetane (**11**) with H_2O_2.[12] Selective protection of the hydroperoxide proceeded in low yield; oxidation of the resulting alcohol afforded the 3-methyl-3-peroxyalkanal (**13**). Attempted homologation of **13** with MeMgBr, MeLi, or MeTi(O*i*Pr)$_3$ resulted only in fragmentation. Although conversion to **10** could be achieved in low yield with Me_3Al,[20] this approach was ultimately abandoned in favor of the route described in Scheme 2.

Peroxyketone **14**, prepared in high yield via perruthenate oxidation of alcohol **10**, was deprotected to furnish a mixture of 1,2-dioxolan-3-ols. These tended to decompose upon chromatography, and the crude product was directly subjected to acid-catalyzed etherification to provide a nearly inseparable 1:1 mixture of *cis*- and *trans*-alkoxydioxolanes **15** (Scheme 4). Treatment of the alkoxydioxolanes with $TiCl_4$ and the trimethylsilyl ketene acetal of ethyl thioacetate furnished a 1:1 mixture of thioesters *cis*-**16** and *trans*-**16**. The derived aldehydes *cis*- and *trans*-**17** were separated and individually oxidized to furnish diastereomerically pure samples of (+)-*cis*- **1a** and (−)-*trans*-**1a**.

(11) Dussault, P. H.; Liu, X. *Org. Lett.* **1999**, *1*, 1391−1393. A related approach to substituted 1,2-dioxolanes based upon Lewis acid mediated reactions of 1,1-bisperoxyacetals has recently been reported: Ramirez, A.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 4617−4620.

(12) Dussault, P. H.; Trullinger, T. K.; Noor-e-Ain, F. *Org. Lett.* **2002**, *4*, 4591−4593.

(13) Portions of this work were reported in doctoral dissertations: Trullinger, T. K. University of Nebraska, Lincoln, NE, 2002. Dai, P. University of Nebraska, Lincoln, NE, 2004.

(14) Bernet, B.; Vasella, A. *Tetrahedron Lett.* **1983**, *24*, 5491−5494.

(15) Based upon ^{19}F NMR of the derived methoxytrifluoromethylphenylacetates: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

(16) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378−1380; Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109−1111.

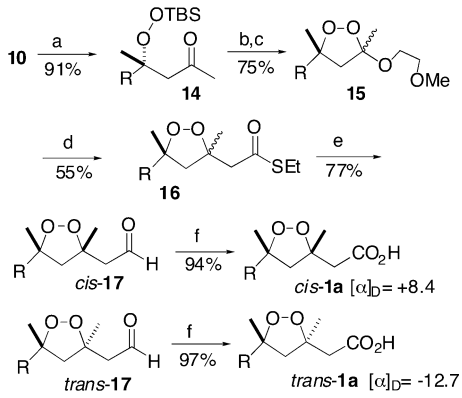
(17) Balsamu, A.; Ceccarelli, G.; Crotti, P.; Macchia, F. *J. Org. Chem.* **1975**, *40*, 473−476.

(18) Picard, P.; LeClerq, D.; Bats, J.-P.; Moulines, J. *Synthesis* **1981**, 550−551.

(19) Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis* **1988**, 862−868.

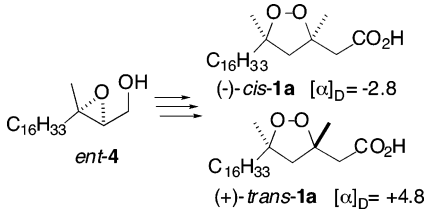
(20) Allen, J. L.; Paquette, K. P.; Porter, N. A. *J. Am. Chem. Soc.* **1998**, *120*, 9362−9363.

SCHEME 4. Synthesis of (+)-*cis*-1a and (−)-*trans*-1a[a]



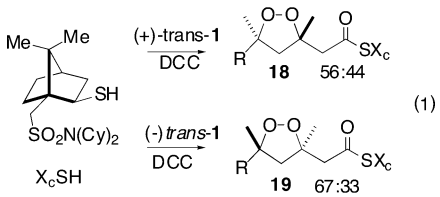
[a] Reagents and conditions: (a) TPAP, NMO; (b) aq HF, CH_3CN/THF; (c) 2-methoxyethanol, HCl (cat.); (d) $TiCl_4$ (1.1 equiv) $H_2C{=}CH_2$(OTMS)SEt (2.5−4 equiv), −50 to 0 °C; (e) DIBAL, CH_2Cl_2, −78 °C; (f) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, *t*-BuOH, 2-methyl-2-propene.

SCHEME 5. Preparation of (−)-*cis*-1a and (+)-*trans*-1a



The enantiomers, (−)-*cis*-**1a** and (+)-*trans*-**1a**, were prepared from *ent*-**4** by an identical route. (Scheme 5).

The disparity in the specific rotations for the two series led us to assess enantiomeric purity of formation of diastereomeric derivatives (eq 1). Our previous research had demonstrated

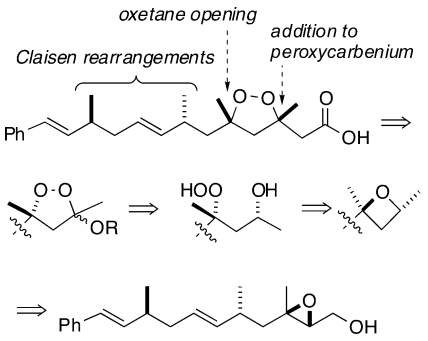


resolution of racemic 3,5,5-trimethyl-1,2-dioxolane acetic acids as diastereomeric thioesters.[21] Application of this method to (+)- and (−)-*trans*-**1a** revealed low and variable stereochemical purity, suggesting that the oxetane openings proceeded with highly inconsistent stereoselectivity.

Lessons from the Model Synthesis: Synthesis of Candidate Structures for Plakinic Acid A. Any synthetic approach to plakinic acid A faced the challenge of controlling both dioxolane and side chain stereocenters. As before, our approach was based upon installation of the 1,2-dioxolane acetic acid via reaction of a thioester silyl ketene acetal with an enantiomerically enriched alkoxydioxolane (Scheme 6). However, drawing upon our experience with the synthesis of **1a**, the crucial oxetane opening would be conducted on a single stereoisomer, using the displaced secondary alcohol as an internal stereochemical marker and resolving agent. The oxetane would arise from an enantiomerically enriched 2,3-epoxy alcohol now containing four stereocenters.

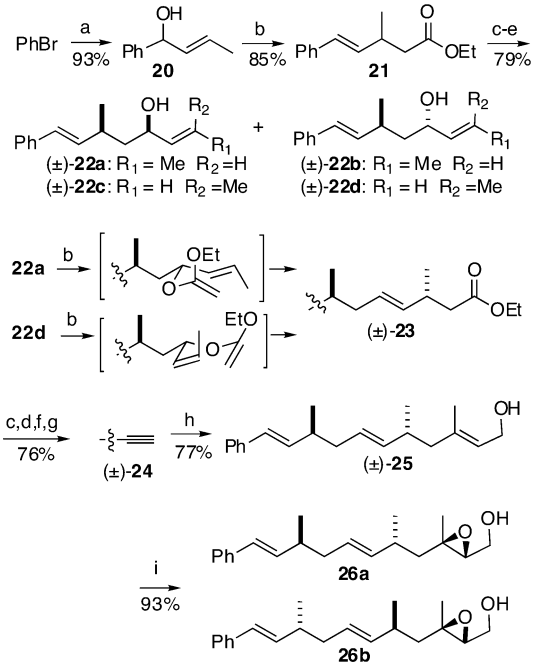
(21) Dussault, P. H.; Trullinger, T. K.; Cho-Shultz, S. *Tetrahedron* **2000**, *56*, 9213−9220.

SCHEME 6. Plakinic Acid A Retrosynthesis[a]



[a] Illustrated for one stereoisomer.

SCHEME 7. Synthesis of Plakinic A Sidechain[a]



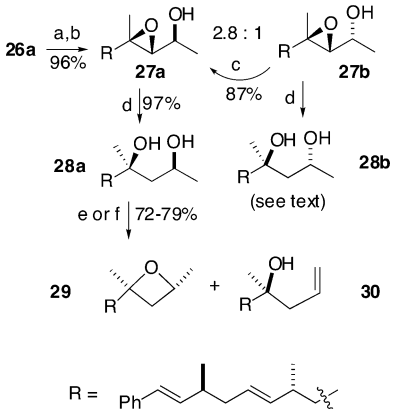
[a] Reagents and conditions: (a) Mg, crotonaldehyde; (b) $(EtO)_3CCH_3$, propionic acid, 140 °C; (c) LAH; (d) Swern; (e) (*E*)-propenyl bromide, *t*-BuLi, THF; (f) Zn, CBr_4, PPh_3; (g) *n*-BuLi; (h) Me_3Al, Cp_2ZrCl_2 then *n*-BuLi, $(CH_2O)_n$; (i) $Ti(OiPr)_4$, (−)-DET, *t*-BuOOH.

The synthesis of the plakinic acid A side chain began with Claisen homologation of allylic alcohol **20** to ester **21** (Scheme 7). Conversion to the corresponding aldehyde, followed by addition of (*E*)-propenyllithium, furnished a 1:1 mixture of diasteromeric allylic alcohols **22a** and **22b**, for which the relative stereochemistry was determined by conversion to 2,4-disubstituted butyrolactones.[22] Alternatively, use of propenylmagnesium bromide as a nucleophile resulted in predominant formation of **22a** and **22b**, along with smaller amounts of the corresponding (*Z*)-allylic alcohols **22c** and **22d**.[23] An iteration of the Claisen/DIBAL sequence on **22a** (or **22d**) produced ester **23**. Homologation of the derived aldehyde furnished alkyne **24**, which underwent carbalumination and trapping with formaldehyde to

(22) Kiyooka, S.-i.; Li, Y.-N.; Shahid, K. A.; Okazaki, M.; Shuto, Y. *Tetrahedron Lett.* **2001**, *42*, 7299−7301. See Supporting Information for details.

(23) Alcohols **22a** and **22d** both underwent the Johnson Claisen reaction to furnish ester **23**, whereas **22b**/**22c** furnished an epimeric ester under the same conditions.

SCHEME 8. Synthesis of Oxetane 29[a]

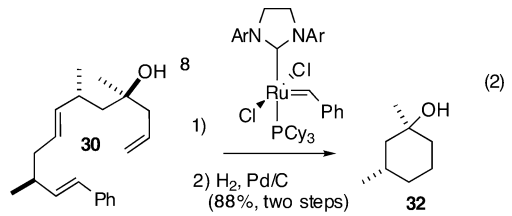


[a] Reagents and conditions: (a) Dess−Martin periodinane; (b) MeMgBr; (c) (1) DEAD, PPh_3, 4-NO_2PhCO_2H, (2) NaOMe, MeOH; (d) Red-Al; (e) TsCl, *t*-BuOK, THF; (f) TsCl, *t*-BuOK; NaH.

furnish racemic alkenol **25**. Asymmetric epoxidation furnished separable diastereomers **26a** and **26b**, each found to be >80% enantiomeric excess.[17] Assignment of stereochemistry for **26a** and **26b** is based upon a subsequent correlation of the C_3 and C_5 centers (vide infra).

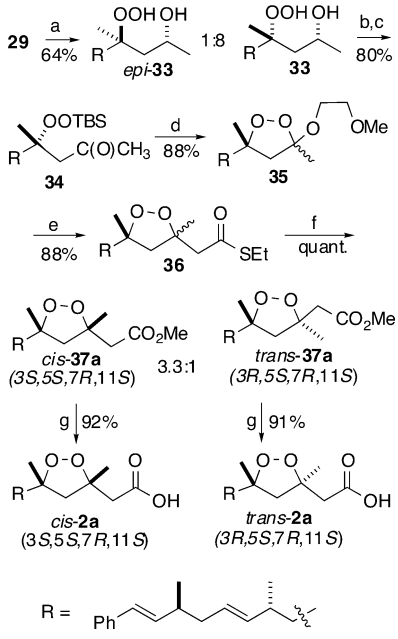
At this point, we chose to carry forward stereoisomer **26a** (Scheme 8). Addition of methylmagnesium bromide to the corresponding epoxyaldehyde furnished a mixture of diastereomeric epoxy alcohols **27a** and **27b**, which after separation were individually reduced to the corresponding 1,3-diols, **28a** and **28b**. For preparative routes, the minor epoxy alcohol **27b** was epimerized to **27a** via a Mitsonobu inversion.[24] The syn stereochemistry of the major diol (**28a**) was confirmed by conversion to the 2,2-dimethyl-1,3-dioxane.[25] Treatment of **28a** with a stoichometric quantity of toluenesulfonyl chloride and excess *t*-BuOK produced a 5:1 mixture of oxetane **29** and alkenol **30**; similar results were obtained upon treatment of the preformed monosulfonate with NaH. *anti*-1,3-Diol **28b** underwent cyclization in much poorer yield, but this problem was rendered moot by the successful epimerization of **27b**.

The presence of multiple alkenes meant that that the byproduct of elimination (**30**) could not be "recycled" to oxetane **29** via iodoetherification as in the model system. However, this byproduct did provide a means to determine the absolute stereochemistry of the side chain stereocenters (eq 2). Ring-closing metathesis of **30** furnished a cyclohexene, which was hydrogenated to furnish the known *cis*-1,3-dimethyl cyclohexanol (**32**).[26,27]



Opening of oxetane **29** with ethereal hydrogen peroxide in the presence of $Yb(OTf)_3$ proceeded at temperatures ≥0 °C to provide a 4:1 ratio of hydroperoxyalkanols **33** and *epi*-**33**

SCHEME 9. Synthesis of *cis*-2a and *trans*-2a[a]



[a] Reagents and conditions: (a) TMSOTf, H_2O_2, ether, −78 °C; (b) LiHMDS, TBSCl; (c) Dess−Martin periodinane; (d) HF, 2-methoxyethanol, 2 days; (e) $TiCl_4$ (1.1 equiv) $H_2C{=}CH_2(OTMS)SEt$ (16 equiv), −50 to 0 °C; (f) NaOMe, MeOH; (g) LiOH, 30% H_2O_2, THF.

(Scheme 9).[12] The use of TMSOTf allowed performance of the same reaction between −78 and 0 °C and reproducibly afforded an 8:1 mixture of **33** and *epi*-**33**, which were easily separated by semipreparative HPLC. The stereochemistry of the major diastereomer was confirmed by reduction (Me_2S) to the diol and correlation with the *syn*-1,3-diol derived from reduction of epoxy alcohol **26b**. Selective silylation and oxidation furnished peroxyketone **34**, which underwent deprotection to provide the 1,2-dioxolane-3-ol. Acidic transetherification, an uneventful reaction in the saturated model, proved problematic, with strongly acidic conditions resulting in fragmentation to non-peroxidic products whose identity would become clear later (vide infra). However, treatment of **34** with HF and 2-methoxyethanol achieved a one-pot conversion to a mixture of *cis*- and *trans*-alkoxydioxolanes (**35**); TLC monitoring suggested this transformation proceeds via a rapid deprotection (<1 h) followed by a much slower transetherification (48 h). Addition of $TiCl_4$ to a solution containing **35** and excess silyl ketene acetal produced a 3.3:1 mixture of *cis*- and *trans*-**36**. The same stereochemical outcome was observed regardless of whether the starting material was *cis*-**35**, *trans*-**35**, or a mixture. The corresponding methyl esters **37** were readily separated and the individual diastereomers saponified to provide the *cis*-(3*S*,5*S*,7*R*,-11*S*) and *trans*-(3*R*,5*S*,7*R*,11*S*) isomers of plakinic acid A (**2**).

In the course of our efforts to convert **35** to **36**, we discovered that premixing the Lewis acid and alkoxydioxolane, the optimal protocol for the saturated series, resulted in the exclusive formation of a nonperoxide product,[28] which proved to be a single diastereomer of a tetrahydrofuranyl ketone **38** (Table 1).

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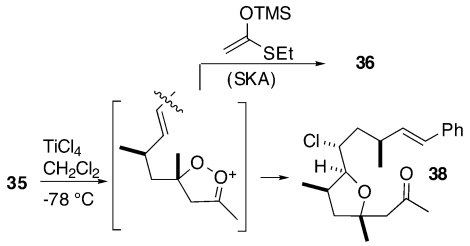
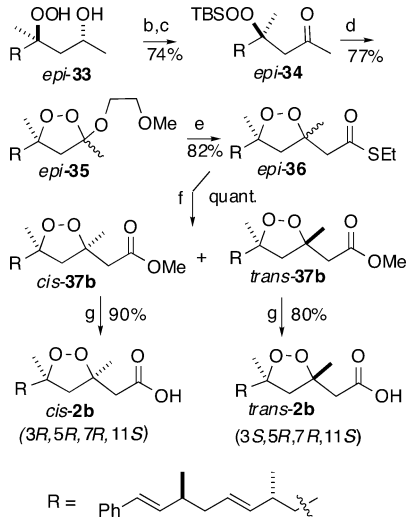
TABLE 1. Inter- versus Intramolecular Reactions



order[a]	SKA (equiv)	[**35**] (M)	**36** (%)	**38** (%)
A	4	0.05		78
B	4	0.05	70	20
B	8	0.05	79	15
B	8	0.2	86	6
B	16	0.2	88	5

[a] A = $TiCl_4$ then SKA; B = SKA then $TiCl_4$.

SCHEME 10. Synthesis of *cis*-2b and *trans*-2b[a]

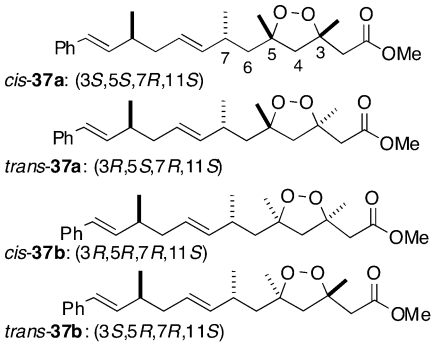


[a] Reagents and conditions: see Scheme 9.

The formation of this byproduct appears to result from intramolecular attack of the side chain alkene on the distal oxygen of the developing peroxycarbenium ion; an analogous reaction may explain the decomposition of **34** (or, more likely, the derived 1,2-dioxan-3-ol) in the presence of strongly acidic conditions. Although peroxides have been shown to undergo 5-*exo* nucleophilic attack on alkene-derived halonium ions,[29] we are unaware of 5-*exo* nucleophilic attack of an alkene on a protonated or complexed peroxide. In contrast, the corresponding 3-*exo* cyclizations are well established.[30] In the end, we found the fragmentation could be minimized by use of higher reactant concentrations and by addition of Lewis acid into a premixed solution containing alkoxydioxolane and excess silyl ketene acetal.

Two additional plakinic A stereoisomers, *trans*-3*S*,5*R*,7*R*,11*S* and *cis*-3*R*,5*R*,7*R*,11*S*, were prepared similarly from hydroperoxyalkanol *epi*-**33b**, the minor product of the oxetane opening (Scheme 10).

Comparison of the chemical shifts and coupling constants of $H_4/H_4'$and H_6/H_6' for the four synthetic isomers and the literature values for plakinic acid methyl ester (Figure 1) suggests the natural product is a *cis*-3,5-disubstituted 1,2-dioxane closely related to *cis*-**37b**.[2]



^{1}H NMR chemical shifts (J values)

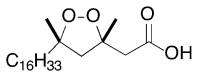
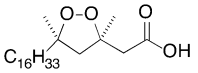
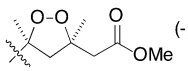
	H_4	$H_{4'}$	H_6	$H_{6'}$	$[\alpha]_D$
cis-**37a**	2.52	2.06	1.63 (14,6)	1.57 (14,8)	+81.5
trans-**37a**	2.42	2.21	1.72 (14,6)	1.57 (14,7)	+14.9
cis-**37b**	2.58	2.11	1.67 (14,8)	1.55 (14,6)	-11.4
trans-**37b**	2.45	2.26	1.78 (14,8)	1.56 (14,5)	+12
2-methyl ester	2.57	2.07	1.66 (14,8)	1.54 (14,6)	-57.8

FIGURE 1. Comparison of selected spectral data

TABLE 2. Comparison of Selected ^{13}C Shifts

peak	**2**-Me ester	*cis*-**37b**
C_2	44.3	44.3
C_3	83.7	83.7
C_4	55.6	55.7
C_5	86.8	86.8
C_6	45.5	45.5
C_{14}	25.2	25.2
C_{15}	23.9	23.9
C_{16}	20.0	20.0
C_{17}	22.7	22.7

TABLE 3. Comparison of Specific Rotations

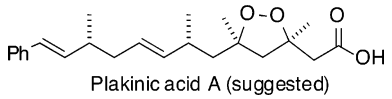
Compound	$[\alpha]_{observed}$	%e.e.	$[\alpha]_D$ calc
 (+)-*cis*-**1a**	+8.4	34	+25
 (-)-*cis*-**1a**	-2.8	12	-23
 (-)-*cis*-**37b**	-11.4	80	-14
Plakinic A methyl ester (**2**-methyl ester)	-57.8	100[a]	-58

[a] Assumed.

The similarity of plakinic acid A and *cis*-**37b** is also evident from a comparison of ^{13}C chemical shifts (Table 2).

Comparison of the specific rotations for (+)-*cis*-**1a**, (−)-*cis*-**1a**, (−)-*cis*-**37b**, and **2**-methyl ester suggests the large and negative specific rotation for the latter is best accommodated by 3*R*,5*R* stereochemistry across the 1,2-dioxolane (Table 3).

Given that plakinic acid A and (−)-*cis*-**37b** appear to share the same 3*R*,5*R* stereochemistry and display nearly identical ^{1}H and ^{13}C chemical shifts in the vicinity of the 1,2-dioxolane subunit, we hypothesize that the two structures differ only at the remote C_{11} stereocenter. The most likely configuration for plakinic acid A is 3*R*,5*R*,7*R*,11*R*:



Plakinic acid A (suggested)

Conclusion

In conclusion, we have described the first asymmetric synthesis of 1,2-dioxolane-3-acetic acids. The core of the approach is the asymmetric synthesis of γ-hydroperoxyalkanols through regiospecific and stereoselective acid-promoted opening of enantiomerically enriched and diastereomerically pure 2,4,4-trisubstituted oxetanes with hydrogen peroxide. The peroxyalkanols are converted to 3-alkoxy-1,2-dioxolanes, which undergo Lewis acid mediated reaction with a silyl ketene acetal to install the 1,2-dioxolane acetic acid headgroup. The strategy is applied to the asymmetric synthesis of the unnamed plakinate **1a** as well as candidate structures for plakinic acid A, allowing an assignment of configuration for this incompletely characterized natural product.

Experimental Section

General procedures are described in Supporting Information. "Standard drying and purification" refers to drying over Na_2SO_4, concentration of the filtrate at 20−50 mmHg, and purification of the residue by flash chromatography using the indicated eluting solvent. Although no safety problems were experienced in the course of this work, standard safety precautions should be employed for all work with organic peroxides or H_2O_2.[31]

(2*E*)-1-Phenylbut-2-en-1-ol (20). Into a flame-dried three-neck round-bottom flask equipped with a condenser and a dropping funnel under N_2 were added ether, Mg turnings, (7.20 g, 300 mmol) and a tiny crystal of I_2. Bromobenzene (23.6 g, 150 mmol, in 40 mL of ether) was added dropwise with reaction initiated by gentle heating (~40 °C). Following completion of addition, the reaction was refluxed for 30 min and then cooled to 0 °C prior to dropwise addition of a solution of crotonaldehyde (8.40 g, 120 mmol) in 40 mL of ether. The reaction was allowed to warm to room temperature and stirred for 30 min prior to quenching with 10% aqueous H_2SO_4 (100 mL) and ice (100 g). The aqueous layer was extracted with ether (3 × 100 mL). The combined organic layers were sequentially washed with saturated aqueous $NaHCO_3$ (250 mL) and brine (250 mL). Standard drying and purification (20% EA/Hex) afforded **20** (16.6 g, 112 mmol, 93%) as a clear pale yellow oil: R_f = 0.50 (30% EA/Hex); ^{1}H NMR δ 7.26−7.46 (5H), 5.75 (m, 2H), 5.15 (d, 1H, 5.5), 2.04 (br. s, 1H), 1.73 (d, 3H, 5.7); ^{13}C NMR δ 143.4, 133.6, 128.5, 127.5, 127.4, 126.2, 75.3, 17.7; FT-IR 3352, 3061, 3028, 2916, 2855, 1492, 1450, 1070, 1003, 965, 753, 698; EI-HRMS calcd for $C_{10}H_{12}O$ (M^+) 148.0888, found 148.0889.

Ethyl (4*E*)-3-methyl-5-phenylpent-4-enoate (21). A solution of propionic acid (289 mg, 3.9 mmol), triethyl orthoacetate (71.4 mL, 63.2 g, 390 mmol), and alkenol **20** (5.77 g, 39 mmol) in xylene (500 mL) was heated to reflux for 6 h. After removal of solvent at reduced pressure, the oily residue was purified by flash chromatography (8% EA/Hex) to afford ester **21** (7.23 g, 33.2 mmol, 85%) as a pale yellow oil: R_f = 0.66 (10% EA/Hex); ^{1}H NMR δ 7.18−7.41 (5H), 6.42 (d, 1H, 15.9), 6.15 (dd, 1H, 15.9, 7.5), 4.13 (q, 3H, 7.1), 2.87 (m, 1H), 2.40 (m, 2H), 1.25 (t, 3H, 7.1), 1.16 (d, 3H, 6.8); ^{13}C NMR δ 172.4, 137.4,134.2, 128.8, 128.4, 127.1, 126.1, 60.2, 41.7, 34.1, 20.2, 14.2; FT-IR ν 3027, 2981, 2933, 1733, 1449, 1369, 1174, 1030, 965, 747, 691; EI-HRMS calcd for $C_{14}H_{18}O_2$ (M^+) 218.1307, found 218.1308.

(2*E*,4*R,6*S**,7E)- and (2*E*,4*S**,6*S**,7*E*)-6-Methyl-8-phenylocta-2,7-dien-4-ol (22a and 22b).** $LiAlH_4$ (2.02 g, 53.3 mmol) was added in small portions to a solution of ester **21** (7.74 g, 35.5 mmol) in THF (200 mL). The mixture was stirred under N_2 for 1 h and then cooled to 0 °C. The reaction mixture was quenched by addition of $Na_2SO_4 \cdot 10H_2O$ (50 g) and the resulting slurry was stirred for 1 h. The filtrate (Celite) was concentrated to furnish a pale yellow oil that was used directly for the next step.

To a −60 °C solution of oxalyl chloride (6.2 mL, 71 mmol) in CH_2Cl_2 (300 mL) under N_2 was added dropwise DMSO (10.3 mL, 142 mmol). The mixture was stirred for 10 min, and then a solution of the alcohol described above was added dropwise as a solution in CH_2Cl_2 (50 mL). The reaction mixture was stirred for 20 min, and then triethylamine (26.5 mL, 190 mmol) was added. After stirring for 10 min, the reaction was allowed to warm to room temperature. The reaction was quenched by addition of H_2O (200 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were sequentially washed with $NaHCO_3$ (200 mL) and brine (200 mL) and then dried over $MgSO_4$. The residue obtained upon filtration and concentration was purified by flash chromatography (10% EA/Hex) to afford the aldehyde (5.19 g, 84% over two steps) as a clear colorless oil: R_f = 0.40 (15% EA/Hex); ^{1}H NMR δ 9.78 (t, 1H, 2.2), 7.18−7.37 (5H), 6.42 (d, 1H, 16.0), 6.16 (dd, 1H, 16.0, 8.6), 2.96 (m, 1H), 2.57 (ddd, 1H, 16.4, 7.2, 2.2), 2.47 (ddd, 1H, 16.4, 6.9, 2.2), 1.19 (d, 3H, 6.9); ^{13}C NMR δ 202.0, 137.5, 133.9, 129.1, 128.5, 127.3, 126.1, 50.3, 31.8, 20.4; FT-IR ν 3032, 2964, 1722, 1453, 700; HRMS calcd for $C_{12}H_{14}O$ (M^+) 174.1045, found 174.1041.

To a solution of (*E*)-1-bromo-1-propene (0.95 g, 8.26 mmol) in 15 mL of THF at −78 °C under N_2 atmosphere was added *t*-BuLi (1.5 M solution in pentane, 11.1 mL, 16.6 mmol) dropwise. After 30 min, aldehyde (1.29 g, 7.41 mmol, in 5 mL of THF) was added dropwise. The reaction was stirred at −78 °C for 10 min, after which the reaction was allowed to warm to room temperature and stirred for 30 min. The reaction was quenched by addition of aqueous 1 M HCl (20 mL). The aqueous layer was extracted with ether (3 × 15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). Standard drying and purification (15% EA/Hex) afforded the syn alcohol *syn*-**22a** (754 mg, 47%) followed by the anti alcohol *anti*-**22b** (730 mg, 46%), both as pale yellow oils. [The relative stereochemical assignments for **22a** and **22b** are based upon conversion to *trans*-2-methyl-4-(*E*-2-propenyl)-butyrolactone (from **22a**) and the cis isomer (from **22b**). Details are provided in Supporting Information.] **Data for 22a:** R_f = 0.34 (20% EA/Hex); ^{1}H NMR δ 7.20−7.40 (5H), 6.45 (d, 1H, 16.0), 6.11 (dd, 1H, 16.0, 8.2), 5.66 (dq, 1H, 15.3, 6.2), 5.52 (dd, 1H, 15.3, 6.9), 4.13 (m, 1H), 2.58 (m, 1H), 1.90 (br. s, 1H), 1.71 (d, 3H, 6.2), 1.71 (ddd, 1H, 13.8, 8.6, 5,5), 1.53 (ddd, 1H, 13.8, 9.0, 4.7), 1.13 (d, 3H, 6.7); ^{13}C NMR δ 137.6, 135.8, 134.5, 128.7, 128.4, 126.8, 126.2, 125.9, 70.8, 44.4, 33.8, 21.1, 17.6; FT-IR ν 3351, 3025, 2965, 1493, 1450, 1371, 1062, 967, 747, 694; HRMS calcd for $C_{15}H_{20}O$ (M^+) 216.1514, found 216.1521. **Data for 22b:** R_f = 0.31 (20% EA/Hex); ^{1}H NMR δ 7.19−7.40 (5H), 6.37 (d, 1H, 16.0), 6.13 (dd, 1H, 16.0, 8.2), 5.70 (dq, 1H, 15.3, 6.4), 5.50 (ddq, 1H, 15.3, 7.2, 1.2), 4.14 (m, 1H), 2.46 (m, 1H), 1.86 (br. s, 1H), 1.74 (dd, 3H, 6.2, 1.2), 1.71 (m, 1H), 1.53 (dt, 1H, 13.2, 6.6), 1.14 (d, 3H, 6.7); ^{13}C NMR δ 137.6, 136.3, 134.1, 128.4, 128.3, 126.9, 126.8, 125.9, 71.3, 44.2, 34.1, 20.8, 17.6; FT-IR ν 3375, 3025, 2966, 2925, 1493, 1450, 1372, 1064, 967, 748, 694; HRMS calcd for $C_{15}H_{20}O$ (M^+) 216.1514, found 216.1517.

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Ethyl (3*R,4E,7S*,8*E*)-3,7-Dimethyl-9-phenylnona-4,8-dienoate (23).** By a process similar to that employed for synthesis of **21**, allylic alcohol **22a** (1.31 g, 6.06 mmol) was converted to **23** (1.47 g, 5.14 mmol, 85%) as a pale yellow oil: $R_f = 0.68$ (10%EA/Hex); ^{1}H NMR δ 7.18−7.40 (5H), 6.36 (d, 1H, 16.0), 6.15 (dd, 1H, 16.0, 7.4), 5.43 (m, 2H), 4.12 (q, 2H, 7.15), 2.66 (m, 1H), 2.00−2.46 (5H), 1.25 (t, 3H, 7.15), 1.08 (d, 3H, 6.7), 1.05 (d, 3H, 6.7); ^{13}C NMR δ 172.4, 137.7, 136.0, 135.8, 128.3, 128.0, 127.1, 126.7, 125.9, 60.0, 41.8, 39.9, 37.0, 33.6, 20.4, 19.6, 14.2; FT-IR ν 3030, 2969, 2932, 1730, 1453, 1374, 1178, 1029, 972, 753, 701; HRMS calcd for $C_{19}H_{26}O_2$ (M^+) 286.1933, found 286.1922.

[(1*E*,3*S,5*E*,7*R**)-3,7-Dimethyldeca-1,5-dien-9-yn-1-yl]benzene (24).** $LiAlH_4$ (1.63 g, 43.2 mmol) was added in small portions to a solution of ester **23** (8.24 g, 28.8 mmol) in THF (100 mL). The mixture was stirred for 1 h at room temperature and then cooled to 0 °C before quenching with $Na_2SO_4 \cdot 10H_2O$ (50 g). The resulting slurry was stirred for 1 h and filtered through Celite. The filtrate was concentrated to afford the alcohol as a pale yellow oil, which was used without further purification.

To a solution of $(COCl)_2$ (3.80 mL, 43.5 mmol) in CH_2Cl_2 (200 mL) under N_2 atmosphere at −60 °C was added dropwise DMSO (6.31 mL, 87 mmol). The mixture was stirred for 10 min, and then a solution of crude alcohol in CH_2Cl_2 (30 mL) was added dropwise. The reaction mixture was stirred for 20 min, and then NEt_3 (24.0 mL, 170 mmol) was added. The mixture was stirred at −60 °C and then warmed to room temperature and quenched with H_2O (150 mL). The separated aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic layers were washed sequentially with $NaHCO_3$ (150 mL) and brine (150 mL). The dried solution (MgSO4) was filtered and concentrated. The residue was purified by flash chromatography (10% EA/Hex) to afford the aldehyde (5.92 g, 24.5 mmol, 85% over two steps) as a pale yellow oil: $R_f = 0.37$ (20% EA/Hex); ^{1}H NMR δ 9.70 (t, 1H, 2.4), 7.17−7.37 (5H), 6.34 (d, 1H, 15.9), 6.11 (dd, 1H, 15.9, 7.5), 5.43 (m, 2H), 2.74 (m, 1H), 2.29−2.46 (3H), 2.10 (m, 2H), 1.07 (d, 3H, 6.6), 1.06 (d, 3H, 6.7); ^{13}C NMR δ 202.6, 137.7, 136.0, 135.7, 128.4, 128.2, 127.69, 126.8, 125.9, 50.4, 39.9, 37.19, 31.6, 20.7, 19.8; FT-IR ν 2955, 2928, 2854, 1722, 1458, 1379, 1271, 1120, 1071, 964, 744, 694; HRMS calcd for $C_{17}H_{22}O$ (M^+) 242.1671, found 242.1680.

To a suspension of Zn dust (681 mg, 10.4 mmol) in CH_2Cl_2 (50 mL) was added CBr_4 (3.46 g, 10.4 mmol) and Ph_3P (2.73 g, 10.4 mmol). The reaction was stirred for 12 h at room temperature, after which was added the aldehyde (1.26 g, 5.21 mmol). The reaction was stirred for 30 min and then poured into pentane (300 mL). The resulting brown cloudy mixture was filtered through Celite and concentrated under vacuum. The residue was purified by flash chromatography to afford the dibromoalkene (1.87 g, 90%) as a pale yellow oil: $R_f = 0.81$ (10%EA/Hex); ^{1}H NMR δ 7.17−7.37 (5H), 6.37 (t, 1H, 7.1), 6.36 (d, 1H, 16.0), 6.14 (dd, 1H, 16.0, 7.5), 5.37 (m, 2H), 2.36 (m, 1H), 2.27 (m, 1H), 2.01−2.20 (4H), 1.09 (d, 3H, 6.7), 1.00 (d, 3H, 6.8); ^{13}C NMR δ 137.8, 137.5, 136.18, 136.16, 128.5, 128.1, 127.8, 126.8, 126.0, 88.8, 40.2, 40.1, 37.3, 36.0, 20.4, 19.9; FT-IR ν 3026, 2959, 2924, 2914, 1600, 1492, 1449, 1374, 964, 775,746, 692.

To a solution of the dibromoalkene (6.16 g, 15.4 mmol) in THF (100 mL) at −78 °C under N_2 was added *n*-BuLi (nominally 2.6 M in hexane, 11.9 mL, 30.9 mmol) over 30 min. The reaction was stirred at −78 °C for 1 h, after which the solution was allowed to warm to room temperature. After 2 h the reaction was cooled to 0 °C and quenched with 3 M HCl (100 mL). The aqueous layer was extracted with ether (2 × 100 mL) and the combined organic layers were washed with saturated $NaHCO_3$ (150 mL) and brine (150 mL). Standard drying and purification (5% EA/Hex) afforded the alkyne **24** (3.31 g, 90% over two steps) as a pale yellow oil: $R_f = 0.73$ (10% EA/Hex); ^{1}H NMR δ 7.17−7.40 (5H), 6.37 (d, 1H, 16.0), 6.18 (dd, 1H, 16.0, 7.4), 5.47 (m, 2H), 2.33−2.44 (2H), 2.05−2.23 (4H), 1.98 (t, 1H, 2.6), 1.11 (d, 3H, 6.7), 1.10 (d, 3H, 6.7); ^{13}C NMR δ 137.9, 136.2, 135.9, 128.4, 128.0, 127.5, 126.8, 126.0, 83.1, 69.2, 40.0, 37.2, 35.82, 26.3, 19.83, 19.79; FT-IR ν 3311, 2924, 2855, 1457, 1377, 1270, 1072, 700; HRMS calcd for $C_{17}H_{22}O$ (M^+) 238.1721, found 238.1723.

(2*E*,5*R,6*E*,9*S**,10*E*)-3,5,9-Trimethyl-11-phenylundeca-2,6,10-trien-1-ol (25).** To a flame-dried three-neck flask was added bis-(cyclopentadienyl) zirconium dichloride (6.14 g, 21 mmol) and CH_2Cl_2 (200 mL). The solution was cooled to 0 °C, after which was slowly added Me_3Al (21.0 mL, nominally 2.0 M in toluene, 42 mmol). After the lemon yellow solution had stirred for 10 min, a solution of alkyne **24** (5.0 g, 21.0 mmol) in CH_2Cl_2 (10 mL) was added over a period of 30 min. The reaction was allowed to warm to room temperature and stirred overnight, resulting in a clear, orange solution. Removal of solvent in vacuo (rotary evaporator, warm water bath) afforded a precipitate that was extracted with dry hexane (4 × 25 mL), with each extract transferred via cannula into a common oven-dried flask. The hexane extracts were cooled to −78 °C and treated with *n*-BuLi (8.4 mL, nominally 2.5 M in hexanes, 21 mmol), resulting in a yellow precipitate that was redissolved by addition of THF (200 mL). After 15 min, the resulting dark-red solution was transferred via cannula into a suspension of paraformaldehyde (3.15 g, 5 equiv) in THF (50 mL). The solution was stirred overnight and then quenched with 3 M HCl. The aqueous layer was extracted with ether (2 × 100 mL). The combined organic layers were washed sequentially with saturated aqueous sodium bicarbonate (200 mL) and brine (200 mL). Standard drying and purification (20% EA/hex) afforded allyl alcohol **25** (4.8 g, 77%) as a pale yellow oil: $R_f = 0.31$ (20% EA/Hex); ^{1}H NMR δ 7.17−7.37 (5H), 6.34 (d, 1H, 16.0), 6.12 (dd, 1H, 16.0, 7.4), 5.31−5.40 (3H), 4.13 (d, 2H, 6.9), 2.29−2.37 (2H), 1.90−2.12 (4H), 1.62 (d, 3H, 0.7), 1.29 (br. s, 1H), 1.07 (d, 3H, 6.7), 0.95 (d, 3H, 6.7); ^{13}C NMR δ 138.3, 137.9, 137.6, 136.4, 128.5, 127.9, 126.8, 126.16, 125.9, 125.0, 59.3, 47.40, 40.03, 37.21, 34.53, 20.36, 19.69, 16.2; FT-IR ν 3363, 3024, 2958, 2923, 1599, 1493, 1452, 1377, 967, 748, 694; HRMS calcd for $C_{20}H_{28}OLi$ (M + Li)$^+$ 291.2330, found 291.2296.

(2*R*,3*R*,5*R*,6*E*,9*S*,10*E*)- and (2*R*,3*R*,5*S*,6*E*,9*R*,10*E*)-2,3-Epoxy-3,5,9-trimethyl-11-phenyl-undeca-6,10-dien-1-ol (26a and 26b). To a −20 °C solution of Ti(O*i*-Pr)$_4$ (2.2 mL, 7.2 mmol) in CH_2Cl_2 (40 mL) containing a few 4 Å molecular sieves was added D-(−)-diethyltartrate (1.76 g, 8.7 mmol) dropwise. Next was added a solution of the allyl alcohol (1.37 g, 4.84 mmol) in a small amount of CH_2Cl_2 over a period of 15−20 min (syringe pump). The solution was stirred for 20 min, after which *tert*-butyl hydroperoxide (2.9 mL, nominally 5 M in nonane, dried for 30 min with 4 Å molecular sieves) was added over 40 min. After the consumption of starting material (TLC), the reaction was quenched by addition of 10% aqueous tartaric acid (excess) and 10% aqueous Na_2SO_3 (10 mL) and stirred until the organic layer clarified, ca. 30 min. The aqueous layer was extracted with ether (3 × 50 mL), and the combined organic layers were washed with brine (100 mL). Standard drying and purification (30% EA/hex) afforded 1.35 g (93%) of a 1:1 mixture of diastereomers that were separated by semipreparative HPLC (17% EA/Hex): **26b** eluted at 38 min whereas **26a** eluted at 49 min; both were pale yellow oils. **Data for 26a:** $R_f = 0.53$ (40%EA/Hex); $[\alpha]_D = -17.1$ ($CHCl_3$, $c = 2.0$) 81% ee determined by ^{1}H NMR of its Mosher ester; ^{1}H NMR δ 7.16−7.37 (5H), 6.33 (d, 1H, 15.9), 6.12 (dd,1H, 15.9, 7.5), 5.41 (dt, 1H, 15.3, 6.9), 5.27 (dd, 1H, 15.3, 8.2), 3.77 (dd, 1H, 12.1, 4.1), 3.61 (dd, 1H, 12.1, 6.9), 2.88 (dd, 1H, 6.9, 4.1), 2.35 (m, 2H), 2.09 (m, 2H), 1.76 (dd, 1H, 13.6, 5.3), 1.67 (br. s, 1H), 1.27 (s, 3H), 1.25 (dd, 1H, 13.6, 9.9), 1.08 (d, 3H, 6.7), 1.00 (d, 3H, 6.7); ^{13}C NMR δ 137.7, 136.9, 136.0, 128.5, 128.2, 127.2, 126.9, 125.9, 63.6, 61.5, 60.5, 46.3, 40.0, 37.3, 34.5, 21.8, 20.1, 16.8; FT-IR ν 3423, 3061, 3027, 2961, 1494, 1453, 1381, 1255, 1026, 970, 750, 698; HRMS calcd for $C_{20}H_{28}O_2Li$ (M + Li)$^+$ 307.2249, found 307.2251. **Data for 26b:** $R_f = 0.49$ (40%EA/Hex); $[\alpha]_D = +28.0$ ($CHCl_3$, c 4.0) 82% ee determined by ^{1}H NMR of the ester formed with (*S*)-Mosher acid chloride: ^{1}H NMR δ 7.17−7.37 (5H), 6.33 (d, 1H, 15.9), 6.14 (dd,-1H, 15.9, 7.4), 5.39 (m, 2H), 3.82 (dd, 1H, 12.1, 4.2), 3.67 (dd,

1H, 12.1, 6.7), 2.94 (dd, 1H, 6.7, 4.2), 2.34 (m, 2H), 2.09 (m, 2H), 1.78 (dd, 1H, 13.8, 6.8), 1.68 (br. s, 1H), 1.28 (s, 3H), 1.25 (dd, 1H, 13.8, 8.6), 1.08 (d, 3H, 6.7), 0.97 (d, 3H, 6.7); ^{13}C NMR δ 137.8, 137.4, 136.2, 128.4, 128.1, 126.8, 126.6, 125.9, 63.0, 61.4, 60.5, 45.8, 40.0, 37.3, 33.8, 20.8, 19.9, 16.7; FT-IR ν 3417, 2963, 2928, 1454, 1382, 1254, 1027, 971, 751, 699; HRMS calcd for $C_{20}H_{28}O_2Li$ $(M + Li)^+$ 307.2249, found 307.2246.

(2*S*,3*R*,4*R*,6*R*,7*E*,10*S*,11*E*)- and (2*R*,3*R*,4*R*,6*R*,7*E*,10*S*,11*E*)-3,4-Epoxy-4,6,10-trimethyl-12-phenyl-dodeca-7,11-dien-2-ol (27a and 27b). To a stirred 0 °C solution of epoxy alcohol **26a** (2.19 g, 7.3 mmol) in CH_2Cl_2 (70 mL) was added pyridine (2.26 mL, 28 mmol). After 10 min, Dess Martin periodinane (4.45 g, 10.5 mmol) was added in one portion. After stirring at 0 °C for 2 h, the reaction was judged complete (TLC) and was quenched with saturated aqueous sodium thiosulfate (100 mL) and saturated sodium bicarbonate (aqueous, 100 mL). The mixture was stirred for 30 min and then extracted with ether (2 × 50 mL). The combined organic layers were dried with Na_2SO_4 and then $MgSO_4$. The concentrated filtrate was purified by elution (8% EA/Hex) through a plug of silica gel to afford the 2,3-epoxyaldehyde (ca. 1.8 g) which was used without further purification.

To a −78 °C solution of MeMgBr (nominally 3 M in ether, 2.89 mmol, 8.7 mmol) in THF (60 mL) was added a solution of the epoxyaldehyde (1.72 g, assume 5.77 mmol) in a small amount of THF over 1 h (syringe pump). After 1 h, the reaction was allowed to warm to room temperature and stirred for an additional 30 min prior to being quenched with saturated aqueous NH_4Cl (20 mL). The separated aqueous layer was extracted with ether (2 × 30 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The procedure was repeated on 700 mg of epoxyaldehyde, and the combined batches were purified by chromatography (22% EA/hex) to afford *syn*-epoxy alcohol **27a** (1.29 g, 71%) followed by *anti*-epoxy alcohol **27b** (0.46 g, 25%) both as pale yellow oils. **Data for 27a:** R_f = 0.38 (30% EA/Hex); $[\alpha]_D$ = +32.3 ($CHCl_3$, *c* 1.0); ^{1}H NMR δ 7.17−7.37 (5H), 6.34 (d, 1H, 16.0), 6.14 (dd, 1H, 16.0, 7.5), 5.40 (m, 2H), 3.70 (dq, 1H, 7.9, 6.3), 2.61 (d, 1H, 7.9), 2.35 (m, 2H), 2.10 (m, 2H), 1.78 (dd, 1H, 13.6, 6.5), 1.36 (s, 3H), 1.35 (d, 3H, 6.3), 1.27 (dd, 1H, 13.6, 8.0), 1.26 (br. s, 1H), 1.08 (d, 3H, 6.6), 1.00 (d, 3H, 6.7); ^{13}C NMR δ 137.8, 137.5, 136.2, 128.4, 128.1, 126.8, 126.5, 125.9, 66.3, 66.2, 60.9, 45.9, 40.0, 37.3, 33.9, 20.9, 20.7, 19.9, 16.8; FT-IR ν 3439, 3025, 2962, 1492, 1452, 1381, 1267 (epoxy), 1060, 966, 945, 925, 747, 694; HRMS calcd for $C_{21}H_{30}O_2Li$ $(M + Li)^+$ 321.2406, found 321.2414. **Data for 27b:** R_f = 0.30 (30% EA/Hex); $[\alpha]_D$ = +27.7 ($CHCl_3$, *c* 1.0); ^{1}H NMR δ 7.16−7.36 (5H), 6.34 (d, 1H, 16.0), 6.13 (dd, 1H, 16.0, 7.5), 5.38 (m, 2H), 3.70 (dq, 1H, 8.0, 6.5), 2.69 (d, 1H, 8.0), 2.33 (m, 2H), 2.10 (m, 2H), 1.78 (dd, 1H, 13.7, 6.7), 1.28 (s, 3H), 1.27 (br. s, 1H), 1.24 (d, 3H, 6.5), 1.24 (1H), 1.08 (d, 3H, 6.9), 0.96 (d, 3H, 6.9); ^{13}C NMR δ 137.8, 137.4, 136.2, 128.4, 128.1, 126.8, 126.6, 125.9, 67.8, 66.9, 61.1, 46.0, 40.0, 37.3, 33.9, 20.7, 19.9, 19.1, 17.3; FT-IR ν 3438, 3025, 2963, 2925, 2869, 1492, 1452, 1382, 1267 (epoxy), 1060, 967, 945, 925, 748, 694; HRMS calcd for $C_{21}H_{30}O_2Li$ $(M + Li)^+$ 321.2406, found 321.2395.

Mitsunobu Inversion of 27b to 27a.[24] To a solution of epoxy alcohol **27b** (90 mg, 0.30 mmol) in toluene (4 mL) were added Ph_3P (94 mg, 0.36 mmol) and *p*-nitrobenzoic acid (60 mg, 0.36 mmol), followed by diethyl azodicarboxylate (63 mg, 0.36 mmol). The reaction was stirred at room temperature for 30 min, after which the cloudy mixture was concentrated. The residue was redissolved in hexane/ether (1:1) and eluted through a plug of silica. The crude *p*-nitrobenzoate (150 mg) was dissolved in MeOH (3 mL) and treated with NaOMe (30 mg). After 20 min, the reaction was quenched by addition of saturated aqueous NH_4Cl (3 mL) and ether (5 mL). The aqueous layer was extracted with ether (2 × 5 mL), and the combined organic layers were washed with brine (10 mL). Standard drying and purification (22% EA/Hex) afforded epoxy alcohol **27a** (78 mg, 87%) identical to the sample described above.

(2*S*,4*R*,6*R*,7*E*,10*S*,11*E*)-4,6,10-Trimethyl-12-phenyl-dodeca-7,11-diene-2,4-diol (28a). To a 0 °C solution of epoxy alcohol **27a** (1.59 g, 5.3 mmol) in THF (70 mL) was dropwise added Red-Al (15 mL, nominally 65 wt % in toluene). After stirring overnight, the reaction was judged complete (TLC) and was quenched by slow addition of excess Rochelle's salt (gas evolution). The mixture was diluted with ethyl acetate (50 mL) and stirred until the layers cleared (ca. 1 h). The separated aqueous layer was extracted with ether (2 × 50 mL), and the combined organic layers were washed with brine (2 × 50 mL). Standard drying and purification (30% EA/hex) afforded diol **28a** (1.54 g, 97%) as a pale yellow oil: R_f = 0.28 (30% EA/Hex); $[\alpha]_D$ = +23.1 ($CHCl_3$, *c* 1.0); ^{1}H NMR δ 7.17−7.36 (5H), 6.33 (d, 1H, 16.0), 6.11 (dd, 1H, 16.0, 7.8), 5.54 (dt, 1H, 15.0, 7.2), 5.40 (dd, 1H, 15.0, 9.2), 4.17 (m, 1H), 4.01 (br. s, 1H), 2.77 (br. s, 1H), 2.37 (m, 2H), 2.12 (m, 2H), 1.80 (dd, 1H, 14.1, 10.5), 1.61 (dd, 1H, 14.6, 10.6), 1.44 (m, 2H), 1.22 (s, 3H), 1.14 (d, 3H, 6.0), 1.08 (d, 3H, 6.7), 0.98 (d, 3H, 6.7); ^{13}C NMR δ 138.7, 137.6, 135.6, 128.9, 128.6, 128.4, 126.9, 126.0, 74.8, 64.6, 50.0, 46.5, 39.9, 37.5, 34.1, 29.3, 23.9, 23.5, 20.2; FT-IR ν 3374, 3025, 2964, 2926, 1493, 1453, 1374, 1329, 1177, 1134, 967, 918, 748, 694; HRMS calcd for $C_{21}H_{32}O_2Li$ $(M + Li)^+$ 323.2562, found 323.2568.

(2*R*,4*R*)-2-[(2*R*,3*E*,6*S*,7*E*)-2,6-Dimethyl-8-phenyl-octa-3,7-dienyl]-2,4-dimethyloxetane (29) and (4*S*,6*R*,7*E*,10*S*,11*E*)-4,6,10-Trimethyl-12-phenyl-dodeca-1,7,11-triene-4-ol (30). To a 0 °C solution of diol **28a** (1.44 g, 4.56 mmol) in THF (80 mL) was added *t*-BuOK (540 mg, 4.82 mmol, one portion) followed by a solution of *p*-TsCl (908 mg, 4.76 mmol) in THF (9 mL) over a period of 30 min. The reaction was stirred for an additional 30 min and then allowed to warm to room temperature. After the consumption of diol **28a**, (TLC, ca. 3 h) the reaction was recooled to 0 °C and treated with NaH (500 mg, 60% dispersion in mineral oil). The reaction was stirred overnight and quenched by addition of water (100 mL). The aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were washed with brine (100 mL). Standard drying and purification (10% EA/Hex) afforded the oxetane **29** (0.99 g, 72%) and trienol **30** (190 mg, 14%), each as pale yellow oils. **Data for 29:** R_f = 0.68 (30% EA/Hex); $[\alpha]_D$ = +20.9 ($CHCl_3$, *c* 1.0); ^{1}H NMR δ 7.16−7.37 (5H), 6.33 (d, 1H, 15.8), 6.14 (dd, 1H, 15.8, 7.6), 5.38 (m, 2H), 4.75 (m, 1H), 2.26−2.40 (3H), 2.04−2.20 (3H), 1.67 (d, 2H, 6.6), 1.44 (s, 3H), 1.35 (d, 3H, 6.0), 1.08 (d, 3H, 6.8), 0.97 (d, 3H, 6.7); ^{13}C NMR δ 138.6, 137.9, 136.3, 131.4, 128.4, 128.0, 126.7, 125.9, 81.5, 71.1, 50.5, 40.5, 40.0, 37.3, 33.0, 26.9, 24.3, 21.6, 19.9; FT-IR ν 3024, 2961, 2921, 1492, 1450, 1374, 1265, 1051 (oxetane), 965, 892, 746, 694; HRMS calcd for $C_{21}H_{30}OLi$ $(M + Li)^+$ 305.2457, found 305.2455. **Data for 30:** R_f = 0.63 (30% EA/Hex); $[\alpha]_D$ = +20.8 ($CHCl_3$, *c* 1.0); ^{1}H NMR δ 7.16−7.37 (5H), 6.33 (d, 1H, 15.9), 6.10 (dd, 1H, 15.9, 7.6), 5.85 (m, 1H), 5.43 (m, 2H), 5.09 (m, 2H), 2.31−2.44 (2H), 2.19 (m, 2H), 2.10 (m, 2H), 2.20 (br. s, 1H), 1.52 (dd, 1H, 14.2, 9.8), 1.44 (dd, 1H, 14.2, 3.8), 1.18 (s, 3H), 1.08 (d, 3H, 6.7), 0.98 (d, 3H, 6.7); ^{13}C NMR δ 139.2, 137.7, 135.9, 134.3, 128.44, 128.36, 127.8, 126.8, 126.0, 118.0, 72.9, 48.2, 47.6, 40.0, 37.5, 33.8, 27.0, 23.4, 20.2; HRMS calcd for $C_{21}H_{30}O$ (M^+) 298.2296, found 298.2291.

(1*R*,5*R*)-1,5-Dimethyl-cyclohexan-1-ol (32). To a 25 mL round-bottom flask covered with foil was added trienol **30** (50 mg, 0.17 mmol, in 15 mL of CH_2Cl_2) and a "second generation" ruthenium carbene (14 mg, 0.017 mmol).[26] The reaction was stirred at room temperature under N_2 atmosphere for 3 h. Silica gel (50 mg) was added, and the solution was concentrated. The residue was loaded onto the top of a column of flash silica and eluted with 15% EA/Hex to afford 1,3-dimethyl-2-cyclohexenol (20 mg, 88%) as a colorless oil: R_f = 0.22 (20% EA/Hex); ^{1}H NMR 5.54−5.64 (2H), 2.68 (br. s, 1H), 1.96−2.18 (2H), 1.75 (m, 1H), 1.33 (s, 3H), 1.16−1.28 (2H), 1.00 (d, 3H, 7.0); ^{13}C NMR δ 134.0, 124.1, 72.3, 44.1, 40.2, 30.3, 29.2, 21.1. The cyclohexenol was hydrogenated over Pd/C to afford *cis*-1,3-dimethylcyclohexanol **32** (21 mg, ∼100%).[32]

(32) Senda, Y.; Ishiyama, J.; Imaizumi, S. *Tetrahedron* **1975**, *31*, 1601−1605.

(2*R*,4*S*,6*R*,7*E*,10*S*,11*E*)- and (2*R*,4*R*,6*R*,7*E*,10*S*,11*E*)-4-Hydroperoxy-12-phenyl-4,6,10-trimethyldodeca-7,11-dien-2-ol (33 and *epi*-33). To a flame-dried round-bottom flask was added oxetane **29** (0.790 g, 2.65 mmol) and fresh prepared H_2O_2/ether (25 mL).[12,33] *CAUTION: Anhydrous solutions of H_2O_2 should be used behind a shield. Unused reagent should never be stored but immediately quenched with a reducing agent such as 10% aqueous Na_2SO_3.* The solution was cooled to −78 °C, and TMSOTf (2.7 mL of 1.0 M solution in THF) was added dropwise. After 45 min, oxetane had disappeared (TLC), and the reaction was quenched with H_2O (25 mL) and 4 drops of BHT solution (0.1 M in CH_2Cl_2). The separated organic layer was washed with water (2 × 25 mL) to remove residual H_2O_2. Standard drying and purification (25% EA/Hex) afforded a pale yellow oil (560 mg, 64%) containing an 8:1 mixture of two diastereomers (analytical HPLC as well as crude NMR) that were separated by semipreparative HPLC (25% EA/Hex). The minor product (*epi*-**33**) eluted at 29 min, followed by **33** at 33 min. **Data for 33:** R_f = 0.38 (30% EA/Hex); $[\alpha]_D$ = +20.0 ($CHCl_3$, *c* 1.0); ^{1}H NMR δ 9.44 (s, 1H, OOH), 7.16−7.36 (5H), 6.32 (d, 1H, 16.0), 6.11 (dd, 1H, 16.0, 7.2), 5.54 (dt, 1H, 15.0, 7.1), 5.40 (dd, 1H, 15.0, 8.7), 4.16 (m, 1H), 2.52 (br. s, 1H, OH), 2.33 (m, 2H), 2.08 (m, 2H), 1.90 (dd, 1H, 15.6, 9.7), 1.61 (d, 1H, 15.6), 1.55 (dd, 1H, 14.2, 7.9), 1.48 (dd, 1H, 14.2, 4.7), 1.28 (s, 3H), 1.18 (d, 3H, 6.1), 1.08 (d, 3H, 6.7), 1.00 (d, 3H, 6.7); ^{13}C NMR δ 138.8, 137.7, 136.0, 128.5, 128.2, 126.9, 126.7, 125.9, 84.6, 64.8, 44.7, 42.4, 40.3, 37.3, 33.3, 24.6, 23.7, 23.5, 20.0; FT-IR ν 3320, 3025, 2963, 2928, 1493, 1453, 1375, 1127, 968, 748, 696; HRMS calcd for $C_{21}H_{32}O_3Li$ (M + Li)$^+$ 339.2507, found 339.2511. **Data for *epi*-33:** R_f = 0.43 (30% EA/Hex); $[\alpha]_D$ = +19.5 ($CHCl_3$, *c* 1.7); ^{1}H NMR (400 MHz) 9.21 (s, 1H, OOH), 7.16−7.37 (5H), 6.33 (d, 1H, 15.9), 6.13 (dd, 1H, 15.9, 7.5), 5.42 (m, 2H), 4.17 (m, 1H), 2.76 (br. s, 1H, OH), 2.28−2.38 (2H), 2.12 (m, 2H), 1.9d (dd, 1H, 15.2, 9.7), 1.74 (dd, 1H, 14.3, 8.9), 1.57 (dd, 1H, 14.3, 3.9), 1.39 (dd, 1H, 15.2, 1.0), 1.28 (d, 3H, 6.2), 1.17 (s, 3H), 1.08 (d, 3H, 6.7), 1.00 (d, 3H, 6.8); ^{13}C NMR δ 139.1, 137.8, 136.2, 128.4, 128.2, 126.8, 126.3, 125.9, 84.3, 64.6, 45.5, 45.3, 40.0, 37.4, 32.8, 24.7, 23.6, 21.8, 20.0; FT-IR ν 3340, 3024, 2960, 1494, 1454, 1376, 1127, 968, 747, 694; HRMS calcd for $C_{21}H_{32}O_3Li$ (M + Li)$^+$ 339.2507, found 339.2509.

(4*S*,6*R*,7*E*,10*S*,11*E*)-4-(*tert*-Butyldimethyl)silylperoxy-12-phenyl-4,6,10-trimethyl Dodeca-7,11-dien-2-one (34). To a 0 °C solution of hydroperoxyalkanol **33a** (441 mg, 1.27 mmol) was added dropwise a solution of $LiN(TMS)_2$ (1.27 mL, nominally 1 M in THF) over a period of ca. 30 min. The reaction was stirred for an additional 5 min, whereupon a solution of *tert*-butyldimethylsilyl chloride (181 mg, 1.27 mmol) in THF (4 mL) was added over a period of 30 min. After an additional 30 min, the reaction was judged complete (TLC) and was quenched with saturated aqueous NH_4Cl (excess). The solution was extracted with ether (2 × 10 mL), and the combined organic extracts were dried with Na_2SO_4 and $MgSO_4$. The filtrate was concentrated and purified by filtration through a short plug of silica gel (10% EA/hex) to afford 587 mg (quant) of the silylperoxyalkanol.

By a procedure similar to that employed for the oxidation of alcohol **26a**, the peroxyalkanol (436 mg, 0.943 mmol) was oxidized to silylperoxyketone **34** (347 mg, 80%) as a pale yellow oil: R_f = 0.62 (20%EA/Hex); $[\alpha]_D$ = +9.8 ($CHCl_3$, *c* 2.6); ^{1}H NMR δ 7.16−7.36 (5H), 6.33 (d, 1H, 16.0), 6.13 (dd, 1H, 16.0, 7.6), 5.35 (m, 2H), 2.74 (d, 1H, 14.1), 2.71 (d, 1H, 14.1), 2.33 (m, 2H), 2.17 (s, 3H), 2.07 (m, 2H), 1.67 (dd, 1H, 14.3, 7.7), 1.59 (dd, 1H, 14.3, 4.9), 1.26 (s, 3H), 1.07 (d, 3H, 6.7), 0.97 (d, 3H, 6.6), 0.94 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR δ 208.1, 139.1, 137.9, 136.3, 128.4, 128.1, 126.8, 126.04, 125.96, 84.4, 50.9, 44.0, 40.0, 37.4, 32.9, 32.1, 26.2, 23.4, 22.3, 20.0, 18.2, −5.48; FT-IR ν 3025, 2956, 2929, 2858, 1710, 1493, 1459, 1359, 1251, 966, 888, 835, 784, 747, 693, 671; HRMS calcd for $C_{27}H_{44}O_3SiLi$ (M + Li)$^+$ 451.3220, found 451.3204.

(3*S*,5*S*)-3-[(2*R*,3*E*,6*S*,7*E*)- and (3*S*,5*R*)-3-[(2*R*,3*E*,6*S*,7*E*)-3,5-Dimethyl-2,6-dimethyl-8-phenyl-octa-3,7-dienyl]-5-(2-methoxyethoxy)-1,2-dioxolane (*cis*-35 and *trans*-35). To a solution of silylperoxy ketone **34** (242 mg, 0.54 mmol) in 2-methoxyethanol (15 mL) in a Teflon bottle was added HF (48 wt % in water, 1 mL, *CAUTION*). Conversion of ketone to an initial product, presumably 1,2-dioxolan-3-ol, was complete in ca. 1 h (TLC). After this initial product had also disappeared (48 h, TLC), the reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL) and diluted with ether (20 mL). The aqueous layer was extracted with ether (2 × 10 mL). Standard drying and purification (15% EA/hex, using silica gel pretreated with 2.5% Et_3N) afforded a 3:2 mixture (NMR) of diastereomeric alkoxydioxolanes (184 mg, 88%) as a pale yellow oil. A small portion of the products was separated by careful flash chromatography (10% EA/Hex) to afford individual samples of *cis*-**35** and *trans*-**35**. **Data for *cis*-35**: R_f = 0.45 (20% EA/Hex); $[\alpha]_D$ = +150° ($CHCl_3$, *c* 1.0); ^{1}H NMR δ 7.16−7.36 (5H), 6.32 (d, 1H, 16.0), 6.12 (dd, 1H, 16.0, 7.6), 5.38 (dt, 1H, 15.2, 6.5), 5.29 (dd, 1H, 15.2, 8.5), 3.73 (m, 1H), 3.61 (m, 2H), 3.51 (m, 1H), 3.39 (s, 3H), 2.58 (d, 1H, 13.3), 2.32 (m, 2H), 2.20 (d, 1H, 13.3), 2.08 (m, 2H), 1.64 (m, 2H), 1.46 (s, 3H), 1.31 (s, 3H), 1.08 (d, 3H, 7.0), 0.99 (d, 3H, 7.0); ^{13}C NMR δ 137.8, 137.6, 136.1, 128.5, 128.2, 126.9, 126.8, 125.9, 108.2, 86.5, 72.2, 61.0, 59.0, 58.6, 44.8, 40.0, 37.3, 34.1, 24.9, 22.7, 20.2, 20.1; FT-IR ν 3025, 2958, 2925, 1493, 1451, 1375, 1307, 1203, 1130, 1073, 966, 748, 694; HRMS calcd for $C_{24}H_{36}O_4Li$ (M + Li)$^+$ 395.2774, found 395.2763. **Data for *trans*-35:** R_f = 0.38 (20% EA/Hex); $[\alpha]_D$ = −41.3° ($CHCl_3$, *c* 0.7); ^{1}H NMR (400 MHz) 7.16−7.36 (5H), 6.32 (d, 1H, 16.0), 6.12 (dd, 1H, 16.0, 7.3), 5.38 (dt, 1H, 15.3, 6.5), 5.29 (dd, 1H, 15.3, 7.3), 3.73 (m, 1H), 3.60 (m, 2H), 3.52 (m, 1H), 3.39 (s, 3H), 2.53 (d, 1H, 12.6), 2.35 (d, 1H, 12.6), 2.31 (m, 2H), 2.07 (m, 2H), 1.72 (dd, 1H, 14.2, 5.5), 1.56 (dd, 1H, 14.2, 7.4), 1.45 (s, 3H), 1.35 (s, 3H), 1.07 (d, 3H, 6.5), 1.02 (d, 3H, 6.7); ^{13}C NMR δ 138.6, 137.8, 136.2, 128.5, 128.1, 126.8, 126.4, 126.0, 108.1, 86.2, 73.2, 60.9, 59.0, 58.8, 46.9, 40.1, 37.3, 33.7, 22.7, 22.4, 20.0, 19.6; FT-IR ν 3025, 2958, 2925, 1493, 1451, 1375, 1307, 1203, 1130, 1073, 966, 748, 694; HRMS calcd for $C_{24}H_{36}O_4Li$ (M + Li)$^+$ 395.2774, found 395.2787.

The relative stereochemistry for *cis*- and *trans*-**35** was assigned through (1) NOE enhancements between the H_4/H_4' and the C_3 and C_5 methyl groups and (2) the chemical shifts of H_4 and H_4' relative to literature reports for similar compounds. Details are provided in Supporting Information.

(3*RS*,5*S*)-3,5-Dimethyl-5-[(2*R*,3*E*,6*S*,7*E*)-2,6-dimethyl-8-phenyl-octa-3,7-dienyl]-1,2-dioxolane-3-acetic Acid, Ethyl Thioester (*cis*- and *trans*-36). To a −78 °C solution containing a mixture of *cis*- and *trans*- **35** (127 mg, 0.33 mmol), and the trimethylsilyl ketene acetal of ethyl thioacetate (466 mg, 2.65 mmol) in CH_2Cl_2 (4 mL) was added $TiCl_4$ (0.36 mL, 1 M in CH_2Cl_2) over 10 min. The solution was stirred for 5 min and then quenched with saturated aqueous $NaHCO_3$ (10 mL) and ether (10 mL). The separated aqueous layer was extracted with ether (2 × 10 mL). Standard drying and purification (10% EA/Hex) afforded an inseparable 3.3:1 mixture (NMR) of *cis*- and *trans*-3-alkanoate dioxolanes **36** (125 mg, 0.167 g, 88%) as a pale yellow oil, accompanied by a small amount of tetrahydrofuranyl ketone **38** (6 mg, 0.017 mmol, 5%), also as a pale yellow oil. **Data for 36:** R_f = 0.29 (10% EA/Hex); ^{1}H NMR δ 7.17−7.35 (5H), 6.34 (d, 1H, 15.9), 6.13 (dd, 1H, 15.9, 7.5), 5.39 (m, 1H), 5.32 (dd, 1H, 15.3, 8.7), 2.81−2.96 (m, 4H), 2.55 (d, 0.77H, 12.6), 2.44 (d, 0.23H, 12.6), 2.28−2.39 (2H), 2.18 (d, 0.23H, 12.6), 2.11 (m, 2H), 2.01 (d, 0.77H, 12.6), 1.56−1.74 (2H), 1.41 (s, 2.3H), 1.40 (s, 0.7H), 1.33 (s, 2.3H), 1.31 (s, 0.7H), 1.26 (t, 3H, 6.7), 1.08 (d, 3H, 6.7), 1.01 (d, 3H, 6.7); ^{13}C NMR δ 196.7, 196.5, 138.4, 137.89, 137.86, 136.25, 136.22, 128.5, 128.2, 126.87, 126.83, 126.6, 126.0, 86.8, 86.7, 84.13, 84.09, 56.7, 56.5, 53.1, 52.7, 46.5, 45.7, 40.0, 37.37, 37.32, 34.0, 33.8, 31.6, 24.9, 24.4, 23.9, 23.66, 23.62, 22.78, 22.73, 22.7, 22.2, 20.1, 14.63, 14.57;

(33) Saito, I.; Nagata, R.; Yuba, K.; Matsuura, T. *Tetrahedron Lett.* **1983**, *24*, 1737−1740.

FT-IR ν 3025, 2963, 2925, 2871, 1686, 1493, 1453, 1375, 1307, 1012, 968, 748, 694; HRMS calcd for $C_{25}H_{36}O_3SLi$ $(M + Li)^+$ 423.2545, found 423.2550. **Data for 38:** ^1H NMR δ 7.17−7.37 (5H), 6.36 (d, 1H, 15.4), 5.98 (dd, 1H, 15.4, 8.0), 3.85 (d, 1H, 7.9, 6.1), 3.54 (dt, 1H, 9.1, 2.0), 2.68 (d, 1H, 14.1), 2.55 (m, 1H), 2.44 (d, 1H, 14.1), 2.21 (s, 3H), 1.30−1.88 (5H), 1.25 (s, 3H), 1.09 (d, 3H, 7.0), 1.03 (d, 3H, 7.0); ^{13}C NMR δ 207.9, 137.6, 135.2, 129.5, 128.5, 126.9, 126.0, 74.4, 72.8, 67.0, 54.6, 41.0, 37.4, 34.2, 32.5, 29.4, 23.9, 21.8, 17.0; FT-IR ν 3025, 2962, 2929, 2872, 1710, 1453, 1376, 968, 749; HRMS calcd for $C_{21}H_{29}O_2Cl$ (M^+) 348.1856, found 348.1848.

(3*S*,5*S*)- and (3R,5*S*)-3,5-Dimethyl-5-[(2*R*,3*E*,6*S*,7*E*)-2,6-dimethyl-8-phenyl-octa-3,7-dienyl]-1,2-dioxolane-3-acetic Acid, Methyl Ester (*cis*-37a) and (*trans*-37a). To a solution of thioesters **36** (31 mg, 0.075 mmol) in MeOH (4 mL) was added sodium methoxide (66 mg, 1.2 mmol). The reaction was stirred until the starting material had disappeared (ca 30 min, TLC) and then quenched with saturated aqueous NH_4Cl (saturated 5 mL). The layers were separated, and the aqueous layer was extracted with ether (2 × 5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The filtered solution was concentrated to afford a 3.3:1 mixture of *cis*- and *trans*-dioxolane methyl esters (30 mg, quant yield) as a pale yellow oil that could be separated by semipreparative HPLC (5% EA/Hex), with *cis*-**37a** (major) eluting at 29 min and *trans*-**37a** (minor) eluting at 31 min. **Data for *cis*-37a**: R_f = 0.53 (20% EA/Hex); $[\alpha]_D$ = +81.5° (CH_2Cl_2, *c* 1.0); ^1H NMR δ 7.16−7.36 (5H), 6.33 (d, 1H, 16.2), 6.12 (dd, 1H, 16.2, 7.6), 5.39 (dt, 1H, 15.2, 6.9), 5.30 (dd, 1H, 15.2, 8.0), 3.68 (s, 3H), 2.72 (d, 1H, 14.3), 2.59 (d, 1H, 14.3), 2.52 (d, 1H, 12.6), 2.36 (m, 1H), 2.30 (m, 1H), 2.09 (m, 2H), 2.06 (d, 1H, 12.6), 1.63 (dd, 1H, 15.3, 5.7), 1.57 (dd, 1H, 15.3, 8.0), 1.42 (s, 3H), 1.33 (s, 3H), 1.08 (d, 3H, 7.0), 1.00 (d, 3H, 7.0); ^{13}C NMR δ 171.1, 137.9, 137.8, 136.2, 128.5, 128.2, 126.83, 126.76, 126.0, 86.7, 83.8, 56.6, 51.6, 45.7, 44.3, 40.0, 37.3, 33.9, 24.7, 23.9, 22.7, 20.0; FT-IR ν 3025, 2957, 2926, 2870, 1738, 1493, 1452, 1375, 1346, 1308, 1210, 1154, 1015, 968, 748, 694; HRMS calcd for $C_{24}H_{34}O_4Li$ $(M + Li)^+$ 393.2617, found 393.2611. **Data for *trans*-37a:** R_f = 0.49 (20% EA/Hex); $[\alpha]_D$ = +14.9° (CH_2Cl_2, *c* 1.0); ^1H NMR δ 7.16−7.36 (5H), 6.33 (d, 1H, 15.8), 6.12 (dd, 1H, 15.8, 7.0), 5.39 (dt, 1H, 16.0, 7.0), 5.31 (dd, 1H, 16.0, 7.5), 3.69 (s, 3H), 2.72 (d, 1H, 14.4), 2.62 (d, 1H, 14.4), 2.42 (d, 1H, 12.6), 2.34 (m, 2H), 2.21 (d, 1H, 12.6), 2.09 (m, 2H), 1.72 (dd, 1H, 14.0, 5.5), 1.57 (dd, 1H, 14.0, 6.7), 1.41 (s, 3H), 1.30 (s, 3H), 1.07 (d, 3H, 6.7), 1.01 (d, 3H, 6.7); ^{13}C NMR δ 171.0, 138.4, 137.9, 136.2, 128.5, 128.1, 126.8, 126.6, 126.0, 86.6, 83.8, 56.7, 51.7, 46.4, 44.0, 40.1, 37.3, 33.7, 24.3, 23.5, 22.7, 20.0; FT-IR ν 3035, 2960, 2926, 1739, 1493, 1453, 1375, 1346, 1213, 970, 749, 695; HRMS calcd for $C_{24}H_{34}O_4Li$ $(M + Li)^+$ 393.2617, found 393.2630. The relative stereochemical assignments for *cis*-**37a** and *trans*-**37a** are based upon NOE and chemical shift correlations similar to those described earlier.

(3*S*,5*S*)-3,5-Dimethyl-5-[(2*R*,3*E*,6*S*,7*E*)-2,6-dimethyl-8-phenyl-octa-3,7-dienyl]-1,2-dioxolane-3-acetic Acid (*cis*-2a). To a 0 °C solution of methyl ester *cis*-**37a** (14.4 mg, 0.037 mmol) in THF/H_2O (4:1, 2 mL) were added H_2O_2 (aqueous 30%, 25 ul) and LiOH (4.5 mg). The reaction was allowed to warm to room temperature and stirred overnight. Aqueous Na_2SO_3 (10%, 2 mL) was added, and the solution was acidified to pH 2 with 10% aqueous HCl. The resulting solution was extracted with ether (2 × 5 mL). Standard drying and purification (10/89/1 EA/Hex/AcOH) afforded *cis*-**2a** (12.8 mg, 92%) as a pale yellow oil: R_f = 0.21 (10/89/1 EA/Hex/AcOH); $[\alpha]_D$ = +91° ($CHCl_3$, *c* 0.6); ^1H NMR δ 7.16−7.36 (5H), 6.32 (d, 1H, 16.0), 6.12 (dd, 1H, 16.0, 7.5), 5.39 (dt, 1H, 15.3, 6.8), 5.28 (dd, 1H, 15.3, 8.2), 2.72 (d, 1H, 14.9), 2.66 (d, 1H, 14.9), 2.47 (d, 1H, 12.6), 2.32 (m, 2H), 2.08 (d, 1H, 12.6), 2.07 (m, 2H), 1.61 (m, 2H), 1.44 (s, 3H), 1.34 (s, 3H), 1.08 (d, 3H, 6.7), 0.99 (d, 3H, 6.7); ^{13}C NMR δ 174.9, 137.8, 137.7, 136.2, 128.5, 128.2, 126.92, 126.86, 125.9, 86.9, 83.7, 56.8, 45.6, 44.1, 40.0, 37.3, 33.9, 24.7, 23.6, 22.7, 20.1; FT-IR ν 3000−3300 (br.), 3024, 2958, 2921, 1709, 1453, 1376, 1307, 968, 748, 695; HRMS calcd for $C_{23}H_{32}O_4Li$ $(M + Li)^+$ 379.2461, found 379.2454.

(3*R*,5*S*)-3,5-Dimethyl-5-[(2*R*,3*E*,6*S*,7*E*)-2,6-dimethyl-8-phenyl-octa-3,7-dienyl]-1,2-dioxolan-3-acetic Acid (*trans*-2a). By similar procedure as described for *cis*-**2a**, *trans*-**37a** (15.0 mg, 0.0389 mmol) was converted to *trans*-**2a** (13.2 mg, 91%) as a pale yellow oil: R_f = 0.21 (10/89/1 EA/Hex/AcOH); $[\alpha]_D$ = +0.8° ($CHCl_3$, *c* 0.7); ^1H NMR δ 7.17−7.35 (5H), 6.33 (d, 1H, 15.9), 6.14 (dd, 1H, 15.9, 7.5), 5.35 (m, 2H), 2.72 (d, 1H, 14.8), 2.66 (d, 1H, 14.8), 2.39 (d, 1H, 12.6), 2.31 (m, 2H), 2.23 (d, 1H, 12.6), 2.09 (m, 2H), 1.73 (dd, 1H, 14.0, 5.5), 1.57 (dd, 1H, 14.0, 7.8), 1.43 (s, 3H), 1.31 (s, 3H), 1.07 (d, 3H, 6.7), 1.00 (d, 3H, 6.7); ^{13}C NMR δ 175.8, 138.3, 138.0, 136.2, 128.5, 128.1, 126.8, 126.6, 125.9, 86.7, 83.7, 56.9, 46.3, 43.9, 40.0, 37.3, 33.7, 24.0, 23.4, 22.7, 20.0; FT-IR ν 3000−3300 (br), 3024, 2957, 2921, 1709, 1453, 1375, 1307, 968, 748, 694; HRMS calcd for $C_{23}H_{32}O_4Li$ $(M + Li)^+$ 379.2461, found 379.2458.

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Supporting Information Available: General experimental procedures; experimental procedures and spectral listings associated with synthesis of *cis*- and *trans*-**1a** and *cis*- and *trans*-**2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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