biosynthesis.[22] A detailed understanding of marine α,ω-bipolar sphingolipids may reveal mechanistic details that pertain to D-sphinganine biosynthesis in other organisms.

Experimental Section

All new compounds were purified by HPLC and gave satisfactory high-resolution mass spectra and ^{1}H NMR. See the Supporting Information for general procedures, CD measurements, and selected NMR spectra and MS results for compounds **5** and **6**.

Compound **4:** A solution of (−)-rhizochalin (**2**, 2 mg)[3] in 2% HCl/anhydrous MeOH (0.5 mL) was heated at 75 °C for 24 h in a sealed tube, after which the solution was cooled and concentrated under a stream of N_2. The residue was subjected to microcolumn chromatography (7 × 65 mm, silica) with elution in two stages: a) MeOH/$CHCl_3$ (1/4) to obtain 1-*O*-methylgalactopyranosides; b) CH_2Cl_2/MeOH/NH_4OH (9/4/1) which provided the ninhydrin-positive product **4** (1.3 mg). DCI-MS (NH_3): *m*/*z*: found, 471.4514 $[M+H]^+$; calcd for $C_{28}H_{59}N_2O_3$, 471.4526.

Compound **5:** A solution of **4** (100 μg, 0.11 μmol) in dry CH_3CN (0.30 mL) was treated with *N*-benzoylimidazole (2.1 μmol) and DBU (0.5 mg, see ref. [9]). The solution was heated at 70 °C for 24 h and allowed to cool to 25 °C over 24 h. Volatiles were removed under a stream of N_2 and the residue subjected to microcolumn chromatography (pipette, silica, EtOAc/*n*-hexane (2/7)) to obtain a nonpolar UV-active fraction (0.3 mg). Final purification was achieved by HPLC (Dynamax, 5 μ silica, 10 × 300 mm, EtOAc/*n*-hexane (3/7), 3.3 mL min^{-1}) to give pure **5** (retention time = 22.0 min). ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.02$ (d, $^3J = 8.3$ Hz, 4H; *ortho*-PhCOO), 7.72 (d, $^3J = 8.3$ Hz, 4H; *ortho*-PhCONH), 7.58–7.38 (m, 12H; aryl H), 6.39, 6.38 (2 × br. d, $^3J = 8.5$ Hz, 2H; NH), 5.21 (2 × m, 2H; H-3/H-26), 4.525 (2 × qdd, $^3J = 8.5$, 7.2, 5.5 Hz, 2H; H-2/H-27), 2.34, 2.33 (2 × t, $^3J = 7.2$ Hz, 4H; H-10/H-12), 1.75 (m, 38H), 1.28 (2 × d, $^3J = 7.2$ Hz, 6H; H-1/H-28); matrix-assisted laser desorption/ionization Fourier transform MS: *m*/*z*: found, 909.5388 $[M+H]^+$; calcd for $C_{56}H_{74}N_2O_7Na$, 909.5394.

Attempted perbenzoylation of **4** (1 mg) using excess BzCl/pyridine (60 or 100 °C) resulted almost exclusively in formation of the bis-oxazoline **6** (≈0.5 mg after HPLC purification (silica, EtOAc/*n*-hexane (1/4), 3.3 mL min^{-1}, retention time = 22 min)). Selected data: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.04$ (2 × m, 2H; H-3/H-26), 5.22 (2 × m, 2H; H-2/H-27), 2.36, 2.35 (2 × t, $^3J = 7.4$ Hz, 4H; H-10/H-12), 1.591, 1.594 (2 × d, $^3J = 6.8$ Hz, 6H; H-1/H-28); DCI-MS (NH_3): *m*/*z* (%): found, 643 (4) $[M+H]^+$, 642.4780 (6) $[M^+]$, 105 (100); calcd for $C_{42}H_{62}N_2O_3$, 642.47604.

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[10] Strictly, compound **4** lacks an axis of rotation due to the presence of the ketone group in an even-numbered carbon chain. Mislow and co-workers comment on the natural tendency for chemists to ascribe a quantitative meaning to asymmetry; for example, molecules such as 1-stearoyl-2,3-dipalmitoylglycerin are described as having "very slight" asymmetry (A. B. Buda, T. Auf der Heyde, K. Mislow, *Angew. Chem.* **1992**, *104*, 1012–1031; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 989–1007). In the present context, one can think of **4** as possessing "very slight" C_{2v} symmetry because, for all intents, the molecule behaves spectroscopically and chemically as a C_{2v} entity, even though improper rotations are absent.
[11] Herein lies a limitation to the CD method as applied to dimeric sphingolipids with the same constitution at each chain terminus and midchain substitution. We can uniquely distinguish all isomers with the same local relative configuration at each end group (for example, all C_{2v} isomers), but cannot distinguish those stereoisomers with different local relative configurations at each end from their counterparts obtained by interchanging end-group configurations.
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Amphoteric Character of 2-Vinyloxiranes: Synthetic Equivalents of β,γ-Unsaturated Aldehydes and a Vinylogous Enolate**

Mark Lautens,* Stéphane G. Ouellet, and Stéphane Raeppel

Oxiranes and 2-vinyloxiranes undergo a number of useful transformations including reactions with nucleophiles[1] and Lewis acid mediated rearrangements.[2] In contrast, the utility of vinyloxiranes as precursors to nucleophilic species has not been established. In this report we describe two reactions of

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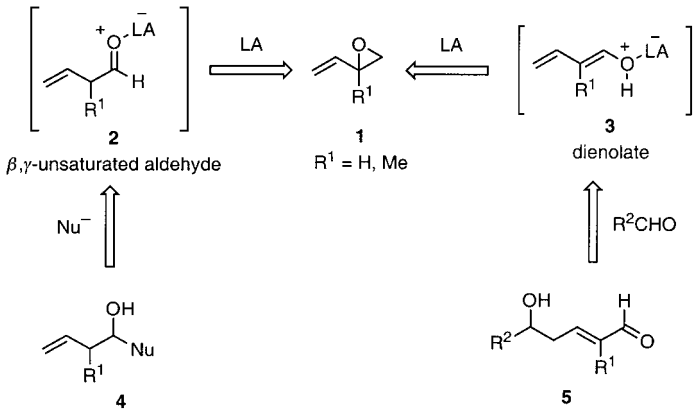
2-vinyloxiranes that reveal their electrophilic and nucleophilic character when treated with a Lewis acid.

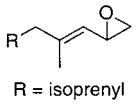
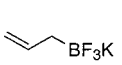
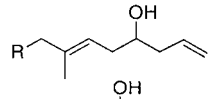
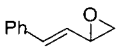
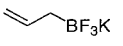
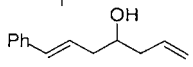
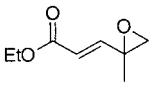
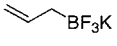
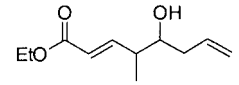
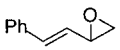
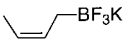
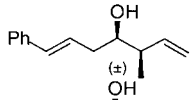
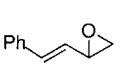
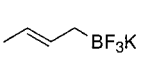
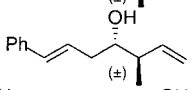
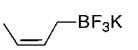
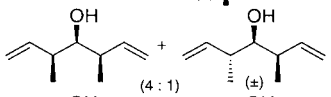
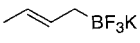
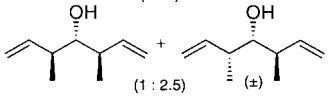
The Lewis acid induced formation of β,γ-unsaturated aldehydes from 2-vinyloxiranes **1** has been reported but very little is known about the utility of the product in subsequent reactions, perhaps due to its instability upon attempted isolation.[3, 4] Our goal was to explore the reactivity of the in situ generated aldehyde **2** (Scheme 1) by selecting a nucleophile that was compatible with the Lewis acid.[2b] The



Scheme 1. Amphoteric character of 2-vinyloxiranes. LA = Lewis acid.

potassium salts of allyl and crotyl trifluoroborate developed by Batey and co-workers[5] served this purpose since $BF_3 \cdot OEt_2$ is a typical additive with these nucleophiles and it is also commonly used in the rearrangement of epoxides.[2a] Our results are summarized in Table 1. We found that allyl, as well as crotyl, trifluoroborates react with various 2-vinyloxiranes.

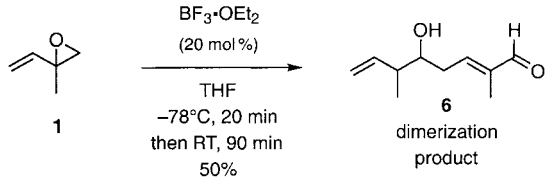
Table 1. Addition of potassium allyl and crotyl trifluoroborates to 2-vinyloxiranes.[a]

Entry	Substrate	Nucleophile	Product(s)[6]	Yield [%][b]
1	 R = isoprenyl			88
2				92
3				72[c]
4				65[d]
5				70[d]
6			 (4 : 1)	74[e]
7			 (1 : 2.5)	78[e]

[a] For typical conditions see the Experimental Section. [b] Yields of isolated product(s). [c] 1:1 Mixture of the *syn* and *anti* cross-coupling products. [d] Only one diastereoisomer was observed. [e] Combined yields.

Both *syn* and *anti* products can be obtained in good yields and with excellent diastereoselectivity by varying the geometry of the nucleophile (entries 4–5). When *E*- and *Z*-crotyl trifluoroborates were reacted with the aldehyde arising from rearrangement of the 2-methyl-2-vinyloxirane, moderate facial selectivity was observed (entries 6–7).

A potentially more important discovery was noted in the absence of an external nucleophile. Upon treatment with $BF_3 \cdot OEt_2$, 2-methyl-2-vinyloxirane (**1**, $R^1 = Me$) dimerized to furnish the δ-hydroxy-α,β-unsaturated aldehyde **6** in 50% yield as an inseparable mixture of two diastereomers [Eq. (1), yield not optimized]. The formation of **6** implies that **1** can rearrange to form a nucleophilic dienolate species as well as the activated aldehyde (Scheme 2). We propose that Lewis acid induced rearrangement of 2-methyl-2-vinyloxirane (**1**, $R^1 = Me$) by a [1,2] hydride shift[7] generates the β,γ-unsaturated aldehyde **2**. This intermediate then enolizes to furnish **3** which reacts with **2** to yield **6**.

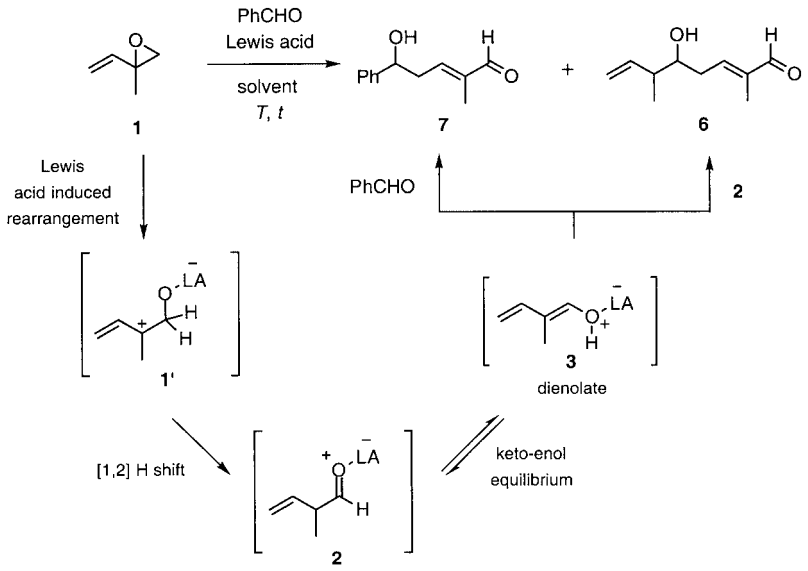


(1)

If this proposal is correct, addition of a different aldehyde would give a cross-aldol adduct. Indeed, when we added one equivalent of benzaldehyde to **1** in the presence of 20 mol% of $BF_3 \cdot OEt_2$, we obtained, after 15 h at room temperature, a mixture composed of dimerized and cross-aldol products **6** and **7** (1:4) in 71% combined yield.[8] With this preliminary result in hand we carried out a study of the parameters that influence this new reaction (nature and amount of Lewis acid, solvent, temperature, etc.) and we have obtained highly selective cross-coupling.

We first examined the effect of the solvent on the coupling between 2-methyl-2-vinyloxirane (**1**, $R^1 = Me$) and benzaldehyde as a model reaction and found that THF gave higher yields and fewer side-products as compared to acetonitrile or diethyl ether. In order to increase the yield and favor the formation of the cross-aldol product **7**, we studied the influence of the Lewis acid (Table 2). The reactions were carried out using an equimolar solution of 2-methyl-2-vinyloxirane and benzaldehyde in THF to which the Lewis acid was added.[9] The results clearly show that aluminum-, boron-, magnesium-, tin-, and scandium-based Lewis acids can catalyze this reaction. The best total yield of **6** and **7** was obtained using either $BF_3 \cdot OEt_2$ or $SnCl_4$ (71% and 73%, respectively) but lower cross-aldol selectivity was observed. The best ratio of **7** to **6** was obtained using 10 mol% of $Sc(OTf)_3$ (OTf = triflate, trifluoromethanesulfonate). The optimal reaction conditions were obtained by premixing the aldehyde (1.0 equiv) and $Sc(OTf)_3$ (10-15 mol%) in THF at $-15\,^{\circ}C$ (cryobath), and

  1433-7851/00/3922-4080 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **2000**, *39*, No. 22



Scheme 2. Proposed mechanism for the formation of **6** and **7** from **1**. The temperature *T* and time *t* values correspond to those of the reactions described in Table 2.

Table 2. Effect of the Lewis acid.[a]

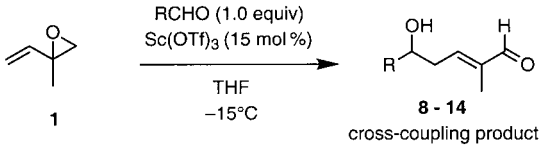
Entry	Lewis acid[b]	*t* [h]	Combined yield [%][c]	Ratio (**7**:**6**)[6]
1	Me_2AlCl in hexanes	2	44	6.7:1
2	$BF_3 \cdot OEt_2$	16	71	4.1:1
3	$MgBr_2 \cdot OEt_2$	15	14	1:0
4	$Sc(OTf)_3$	1	49	12.4:1
5	$SnCl_4$	3	73	2.9:1

[a] All reactions were run at 0.23 M concentrations using distilled PhCHO (1.0 equiv) in dry THF under nitrogen at 0 °C for 10 min and then warmed to room temperature, except for entry 4 which was kept at 0 °C throughout the reaction. [b] 0.2 equivalents of the Lewis acid was used in each case, except in entry 4 where 0.1 equivalents were used. [c] Combined yield of isolated products.

by adding a slight excess of 2-methyl-2-vinyloxirane (**1**, R^1 = Me; 1.3 equiv) in THF with a syringe pump over 1 h. Slow addition of the 2-vinyloxirane significantly reduced the amount of dimerization product. We did not observe the formation of compound **7** below −20 °C or with a catalyst loading lower than 10 mol %.

We tried different aryl aldehydes under the optimized conditions (Table 3) and obtained the cross-coupled products

Table 3. Effect of different electrophiles in the reaction shown in Equation (2).[a]



(2)

Entry	Electrophiles	Products[6]	Yield [%][b]
1	4-nitrobenzaldehyde	**8**	88
2	2-nitrobenzaldehyde	**9**	73
3	4-cyanobenzaldehyde	**10**	90
4	4-bromobenzaldehyde	**11**	78
5	4-methoxybenzaldehyde	**12**	55
6	2-furaldehyde	**13**	97
7	cinnamaldehyde	**14**	91[8]

[a] For typical conditions see the Experimental Section. [b] Yield of isolated product.

in moderate to excellent yields. The mild reaction conditions are compatible with a large range of substituents on the aromatic ring (entries 1–5). Moreover, a heteroaromatic ring (entry 6) and conjugated aldehyde (entry 7) worked well. On the other hand, benzaldehyde derivatives bearing an acidic proton (such as carboxylic acid and hydroxy moieties) did not afford the desired cross-aldol products. Blocking these sites (as the methyl ester and silylether, respectively) resulted in an efficient reaction. Likewise, easily enolizable aliphatic aldehydes led to cross-aldol products, albeit in lower yield.[10]

For the first time, the amphoteric character of 2-vinyloxiranes has been disclosed. We found that 2-vinyloxiranes are a synthetic equivalent of β,γ-unsaturated aldehydes,[11] and that the potassium salts of allyl and crotyl trifluoroborates were suitable nucleophiles for in situ addition reactions. We also demonstrated that 2-methyl-2-vinyloxirane reacts with *E*- and *Z*-crotylborates with moderate selectivity. We are currently investigating the scope of this transformation with a variety of different nucleophiles.[12] We also found that 2-methyl-2-vinyloxirane, upon treatment with an appropriate Lewis acid, can act as a nucleophile and add to various aldehydes. This transformation constitutes a convenient and efficient alternative to the use of a silyl dienol ether, prepared from tiglic aldehyde,[13] in the vinylogous Mukaiyama aldol reaction.[14]

Experimental Section

(±)-(*E*)-1-Phenyl-1,6-heptadien-4-ol: Potassium allyltrifluoroborate salt (232 mg, 1.568 mmol, 1.5 equiv) and $BF_3.OEt_2$ (13 μL, 0.105 mmol, 10 mol %) were successively added to a solution of (*E*)-2-phenyl-2-vinyloxirane (153 mg, 1.047 mmol, 1.0 equiv) in anhydrous THF (10 mL) at 0 °C, and the suspension was stirred at 0 °C for 30 min. The reaction mixture was quenched with an aqueous saturated solution of NH_4Cl, diluted with AcOEt, and extracted three times (3 × 50 mL AcOEt). The combined organic layers were successively washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated. The crude residue was purified by flash chromatography on silica gel (AcOEt/hexanes 10/90) to give the desired product (174 mg, 0.924 mmol, 88 % yield) as a colorless oil. R_f = 0.30 (AcOEt/hexanes 20/80); IR (neat): $\tilde{\nu}$ = 3386 cm^{-1} (br.), 3026, 2928, 1641, 1494, 1433, 966, 744, 693; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.19 (m, 5H; phenyl), 6.49 (d, 1H, *J* = 15.9 Hz; H-1), 6.25 (dt, 1H, *J* = 15.7, 7.3 Hz; H-2), 5.93–5.80 (m, 1H; H-6), 5.16 (d, 1H, *J* = 17.5 Hz; H-7), 5.15 (d, 1H, *J* = 11.1 Hz; H-7), 3.84–3.75 (m, 1H; H-4), 2.50–2.19 (m, 4H; H-3 and H-5), 1.75 (d, 1H, *J* = 3.6 Hz; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.3, 134.6, 133.1, 128.5, 127.2, 126.1, 126.0, 118.0, 70.2, 41.3, 40.4; MS: *m*/*z* (%) = 188 (10) [M^+], 170 (15), 147 (20), 129 (30), 118 (100), 104 (25), 91 (40); HR-MS: calcd for $C_{13}H_{16}O$ = 188.1201, found = 188.1207; molecular formula: $C_{13}H_{16}O$ (188.26 g mol^{-1}).

(*E*)-5-Hydroxy-2-methyl-5-(4-nitrophenyl)-2-penten-1-al (**8**): A solution of $Sc(OTf)_3$ (73 mg, 0.149 mmol, 15 mol %) and 4-nitrobenzaldehyde (150 mg, 0.993 mmol, 1.0 equiv) in anhydrous THF (5 mL) was stirred at −15 °C (cryobath) under argon, and a solution of 2-methyl-2-vinyloxirane (127 μL, 1.290 mmol, 1.3 equiv) in anhydrous THF (2 mL) was slowly added with a syringe pump over 70 min. The reaction mixture was stirred for a further 2 h at −15 °C, quenched with an aqueous saturated solution of $NaHCO_3$ and diluted with Et_2O. The organic layer was successively washed with H_2O and brine, dried over anhydrous Na_2SO_4, decolorized over charcoal, filtered through celite, and concentrated. The crude residue was

purified by flash chromatography on silica gel (Et_2O/hexanes 50/50 →100/0) to give the desired product (205 mg, 0.871 mmol, 88% yield) as a pale yellow oil. $R_f = 0.27$ (Et_2O/hexanes 90/10); IR (neat): $\tilde{\nu} = 3506.1\ cm^{-1}$ (br.), 3115.9, 2921.6, 2710.9, 1692.9, 1648.3, 1605.4, 1512.0, 1404.1, 1345.1, 1237.9, 1106.8, 1063.1, 1019.7, 850.8; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.43$ (s, 1H; H-1), AB signals (4H, $\delta = 8.25$, 7.58, $J_{AB} = 8.7$ Hz; aromatic H), 6.56 (tq, 1H, $J = 7.2$, 1.2 Hz; H-3), 5.07 (dd, 1H, $J = 6.2$ Hz; H-5), 2.89 – 2.77 (m, 2H; H-4), 2.20 (br. s, 1H; OH), 1.71 (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 195.17$, 150.94, 148.99, 147.25, 141.35, 126.46, 123.73, 71.90, 38.37, 9.31; MS: m/z (%) = 218.22 (3.5) [$M^+ - OH$], 152.15 (57.5), 84.13 (100.0); HR-MS: calcd for $C_{12}H_{14}NO_4 = 236.0923$, found = 236.0921; molecular formula: $C_{12}H_{13}NO_4$ (235.23 g mol^{-1}).

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Total Synthesis of (+)-Eurylene and (+)-14-Deacetyleurylene**

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Recently biologically active and structurally novel triterpene polyethers, natural products which are thought to be biogenetically derived from squalene, have been isolated from both marine and terrestrial plants. Among the polyethers are cytotoxic eurylene (**1**) and 14-deacetyleurylene (**2**; see Scheme 1), isolated from the wood of *Eurycoma longifolia* by Itokawa et al.[1] The stereostructures and conformations of **1** and **2** have been elucidated by X-ray crystallographic analysis and spectroscopic methods.[2] The mechanism of action for the cytotoxic activities of these natural polyethers, however, remains to be clarified, because these molecules are available only in restricted amounts from natural sources. Therefore, the development of an efficient synthesis was desired for these polyethers. The novel structures, the cytotoxic activities, and the conformation – activity relationships[2] of **1** and **2** have attracted the attention of many synthetic organic chemists; however, the total synthesis of **2** with potent cytotoxic activity has never been accomplished.[3] Here we report the efficient and stereoselective total synthesis of (+)-eurylene (**1**) and (+)-14-deacetyl eurylene (**2**), featuring monool- and diol-differentiated chemoselective oxidative cyclizations promoted by rhenium(VII) and chromium(VI) oxo species, respectively.

Our retrosynthetic analysis of **1** and **2** is depicted in Scheme 1. The key events for the total synthesis are the stereoselective construction of the *trans* and *cis* tetrahydrofuran (THF) rings and the differentiation of the 14-hydroxy group. To solve this problem, we focused on the hydroxy-directed *syn* oxidative cyclization of acyclic bishomoallylic alcohols promoted by rhenium(VII)[4] and chromium(VI) oxides.[5] Thus, the *trans* THF ring will be constructed by applying our Re^{VII} protocol[6] to the bishomoallylic monool moiety in triol **3**, while the *cis* THF ring is constructed by the Cr^{VI}-induced *cis*-selective cyclization of the bishomoallylic vicinal diol. The pseudo-*meso* triol **3** will, in turn, be derived

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