and CH_2), 1.92 (m, 1 H, CHC=CCCO$_2$), 2.90 (m, 1 H, CHCO$_2$), 3.66 (s, 3 H, OCH_3), 5.35 (dd, J = 15.6, 8.4, Hz, 1 H, C=CHCCO$_2$), 5.46 (dd, J = 15.6, 6.3, Hz, 1 H, CH=CCCO$_2$); ^{13}C NMR ($CDCl_3$) δ 13.86, 22.35, 25.95, 26.12, 29.21, 32.41, 32.81, 32.86, 40.50, 49.21, 51.50, 125.21, 139.08, 175.26; high-resolution MS m/z 238.1915 (calcd for $C_{15}H_{26}O_2$ 238.1933). The purity of the ester by GC (30-m DB-1701 silica capillary column, 150 °C) was 99%.

Methyl (*E*)-2-Methyl-2-heptenoate (14-1). Into a dry, two-neck flask equipped with a magnetic stirrer and a thermometer were placed 11-1 (0.23 g, 1.0 mmol) and dry THF (2.0 mL). To this was added dropwise at 0 °C a 1 M solution of n-Bu_4NF (1.1 mL, Aldrich) in THF. The mixture was stirred at 0 °C for 1 h, treated with H_2O (1.0 mL), stirred for 15 min, and then was poured into a separatory funnel containing a mixture of pentane (20 mL), a saturated solution of NH_4Cl (20 mL), and crushed ice (~20 g). The phases were separated, and the organic phase was washed with 5% HCl (2 × 10 mL) and brine (2 × 20 mL), dried ($MgSO_4$), and concentrated. Distillation (Kugelrohr) afforded 0.12 g (75%) of 14-1: bp 65–70 °C (2 mmHg); $n^{25}$$_D$ 1.4433; IR (neat) 1720 (C=O), 1650 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6.9 Hz, 3 H, CH_3), 1.40 (m, 4 H, CH_2), 1.82 (s, 3 H, C=CCH_3), 2.18 (m, 2 H, CH_2C=C), 3.73 (s, 3 H, OCH_3), 6.77 (t, J = 7.5 Hz, 1 H, CH=C); ^{13}C NMR ($CDCl_3$) δ 12.28, 13.82, 22.37, 28.31, 30.65, 51.57, 127.34, 142.71, 168.68; high-resolution MS m/z 156.1150 (calcd for $C_9H_{16}O_2$ 156.1150). No ^{13}C NMR signals assignable to the Z isomer could be detected. The purity of the ester by GC (30-m SE-54 silica capillary column, 150 °C) was 97%.

Methyl (*E*)-2-Butyl-2-heptenoate (14-2). Following the above procedure for the preparation of 14-1, a 1 M solution of n-Bu_4NF (1.6 mL, Aldrich) in THF was added to the E ester 11-2 (0.41 g, 1.5 mmol) in THF (3.0 mL). The mixture was stirred at 0 °C for 1 h, treated with H_2O (1.5 mL), and stirred for 15 min. Workup and distillation (Kugelrohr) yielded 0.2 g (74%) of a 96:4 mixture of 14-2 and 13-2: bp 72–74 °C (2 mmHg); $n^{24}$$_D$ 1.4482; IR (neat) 1710 (C=O), 1640 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 6 H, CH_3), 1.33 (m, 8 H, CH_2), 2.15 (m, 2 H, C=CCH_2), 2.30 (m, 2 H, C=CCH_2), 3.72 (s, 3 H, OCH_3), 6.75 (t, J = 7.5 Hz, 1 H, CH=C); ^{13}C NMR ($CDCl_3$) δ 13.83, 13.88, 22.43, 22.64, 26.50, 28.19, 31.00, 31.54, 51.45, 132.37, 142.65, 168.53; high-resolution MS m/z 198.1616 (calcd for $C_{12}H_{22}O_2$ 198.1620). The purity of the ester by GC (30-m SE-54 silica capillary column, 160 °C) was 94%.

Methyl (*E*)-2-Butyl-4-cyclohexyl-2-butenoate (14-4). Following the above procedure for the preparation of 14-1, a 1 M solution of n-Bu_4NF (1.1 mL, Aldrich) in THF was added to the E ester 11-4 (0.31 g, 1.0 mmol) in THF (2.0 mL). The mixture was stirred at 0 °C for 1 h, treated with H_2O (1.0 mL), and stirred for 15 min. Workup and distillation (Kugelrohr) yielded 0.20 g (84%) of a 98:2 mixture of 14-4 and 13-4: bp 105–110 °C (0.5 mmHg); $n^{23}$$_D$ 1.4760; IR (neat) 1710 (C=O), 1640 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80–1.80 (m, 18 H, cyclohexyl and C_3H_7), 2.05 (t, J = 7.5 Hz, 2 H, CH_2CCO), 2.27 (m, 2 H, CH_2C=C), 3.71 (s, 3 H, OCH_3), 6.75 (t, J = 7.5 Hz, 1 H, CH=C); ^{13}C NMR ($CDCl_3$) δ 13.87, 22.63, 26.20, 26.30, 26.49, 31.43, 33.24, 36.20, 37.83, 51.42, 132.74, 141.49, 168.41; high-resolution MS m/z 238.1932 (calcd for $C_{15}H_{26}O_2$ 238.1933). The purity of the ester by GC (30-m DB-210 silica capillary column, 170 °C) was 97%.

Methyl (*E*)-3-*n*-Butyl-4-(methoxycarbonyl)-4-nonenoate (20). To a solution of 3a (0.87 g, 4.1 mmol) in THF (8 mL) cooled in an ice–water bath was added a 1.0 M solution of n-Bu_4NF in THF (4.5 mL). The mixture was stirred at ~4 °C for 1 h, treated with H_2O (4 mL), stirred for 15 min at ~4 °C, and then poured into a separatory funnel containing a mixture of pentane, a saturated solution of NH_4Cl, and crushed ice (~20 g). The phases were separated, the aqueous phase was extracted with pentane (80 mL), and the combined organic phases were washed with 5% HCl (2 × 20 mL) and brine (2 × 20 mL), dried ($MgSO_4$), and concentrated. Purification of the residue (90% yield) by flash column chromatography[27] on silica gel using methylene chloride as eluant afforded the diester 20 (58%): bp 76–78 °C (5 × 10^{-3} mmHg); $n^{26}$$_D$ 1.4550; IR (neat) 1730, 1700 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7.2 Hz, 3 H, CH_3), 0.90 (t, J = 6.9 Hz, 3 H, CH_3), 1.05–1.80 (m, 10 H, CH_2), 2.22 (m, 2 H, CH_2C=C), 2.56 (dd, J = 15, 6.6 Hz, 1 H, CHCO$_2$), 2.69 (dd, J = 15, 8.4 Hz, 1 H, CHCO$_2$), 3.10 (m, 1 H, CHCCO$_2$), 3.60 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 6.78 (t, J = 7.5 Hz, 1 H, CH=C); ^{13}C NMR ($CDCl_3$) δ 13.73, 13.81, 22.39, 22.52, 28.06, 29.94, 30.98, 32.93, 34.96, 38.63, 51.08, 51.14, 132.86, 144.92, 167.35, 173.25; high-resolution (FAB) GC–MS (M + H)$^+$ of the main peak 285.2068 (calcd for $C_{16}H_{29}O_4$ 285.2067). GC analysis (30-m DB-210 silica capillary column, 180 °C) of the distillate revealed that the compound was ~90% pure.

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Supplementary Material Available: High-field ^{1}H NMR spectra for 1b, 1c, 3b, 3c, 4c, 6b, 5a, 5b, 7a, 11-1, 11-2, 11-3, 11-4, 13-1, 13-2, 13-4, 14-1, 14-2, 14-4, and 20 (20 pages). Ordering information is given on any current masthead page.

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Enantioselective Total Synthesis of the Mycotoxin (-)-Talaromycin B by a Hetero Diels–Alder Reaction[1]

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(-)-Talaromycin B was formed in an overall yield of 5% in nine steps via a hetero Diels–Alder reaction of the exocyclic vinyl ether 3 and methyl *O*-benzoyldiformylacetate (4) as the key transformation. The enantiomerically pure vinyl ether 3 was prepared in 28% yield and ee >98% by alkylation of the *N*-butyryloxazolidinone 5 with 1-bromo-4-(trimethylsilyl)-2-butyne (6), followed by a reduction–hydrogenation–protodesilylation sequence to give 9, which was transformed into 3 by iodoetherification with iodine and elimination with DBU. Methyl *O*-benzoyldiformylacetate (4) was synthesized by formylation of methyl 3,3-dimethoxypropionate, followed by benzoylation. The cycloaddition of 3 and 4 gave predominantly the desired adduct 11 together with the other three possible diastereomers. (-)-Talaromycin B (2) was obtained from 11 by reduction with DIBAL-H and stereoselective hydrogenation with platinum as catalyst. For purification purposes, 2 was transformed into a cyclic silyl ether by reaction with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane.

The highly toxic mycotoxins talaromycin A (1) and B (2) were discovered by Lynn[2] in 1982 as the first spiroacetals of fungal origin. This unique structural feature occurs in many natural products, e.g., polyether antibiotics,

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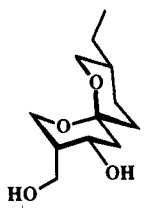

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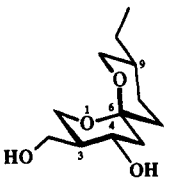
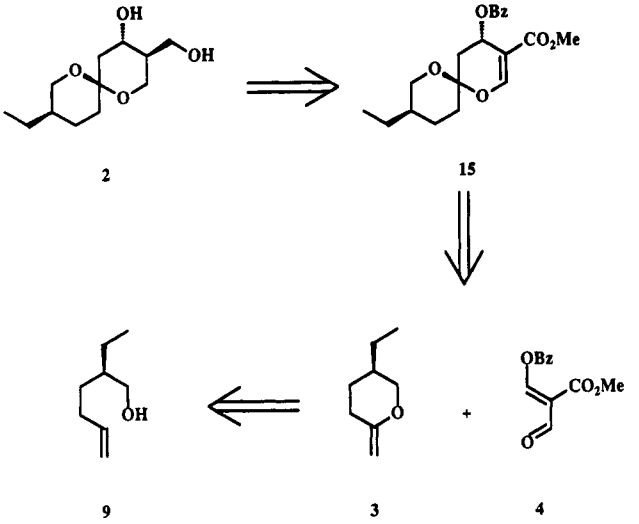


2

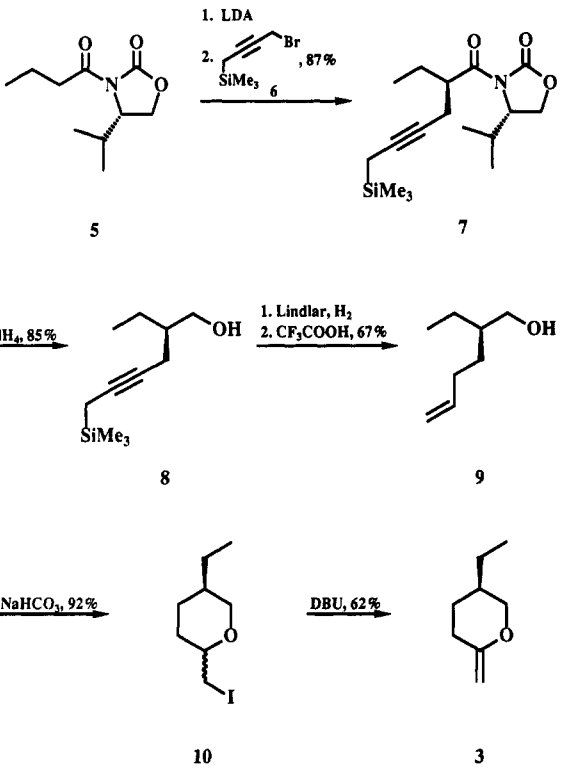
pheromones, milbemycins, and avermectins, which show a broad range of biological and pharmacological activities.[3] Accordingly, synthetic approaches to spiroacetals have been intensively studied in recent years.[4] We report herein a short and enantioselective synthesis of (-)-talaromycin B (2) that requires only nine steps and provides the natural product in an overall yield of 5%.[5] The key step in the synthesis is a hetero Diels–Alder reaction[6] of exocyclic vinyl ether 3 and methyl *O*-benzoyldiformylacetate (4), which allows construction of the spiroacetal moiety[7] with all the necessary carbon atoms in one step (Scheme I). The oxa-1,3-butadiene 4, easily accessible by formylation[8] of methyl 3,3-dimethoxypropionate[9] followed by benzoylation, is a versatile substrate for Diels–Alder

Scheme I. Retrosynthesis of (-)-Talaromycin B (2)



2 15 9 3 4

Scheme II. Synthesis of Vinyl Ether 3



5 7 8 9 10 3

reactions. Together with analogous compounds, 4 has proved useful in the synthesis of 3,4-dihydropyrans, as we have demonstrated.[10]

Vinyl ether 3 bearing the correct absolute stereochemistry (9*R*) was prepared in an overall yield of 28% via 7 according to the Evans[11] methodology (Scheme II). Attempts to introduce the 3-butenyl group by direct alkylation of 5 with 4-bromo-1-butene were not successful due to the well-known low nucleophilicy[12] of *N*-acyloxazolidinone enolates. We circumvented this problem by employing 1-bromo-4-(trimethylsilyl)-2-butyne (6)[13] as the

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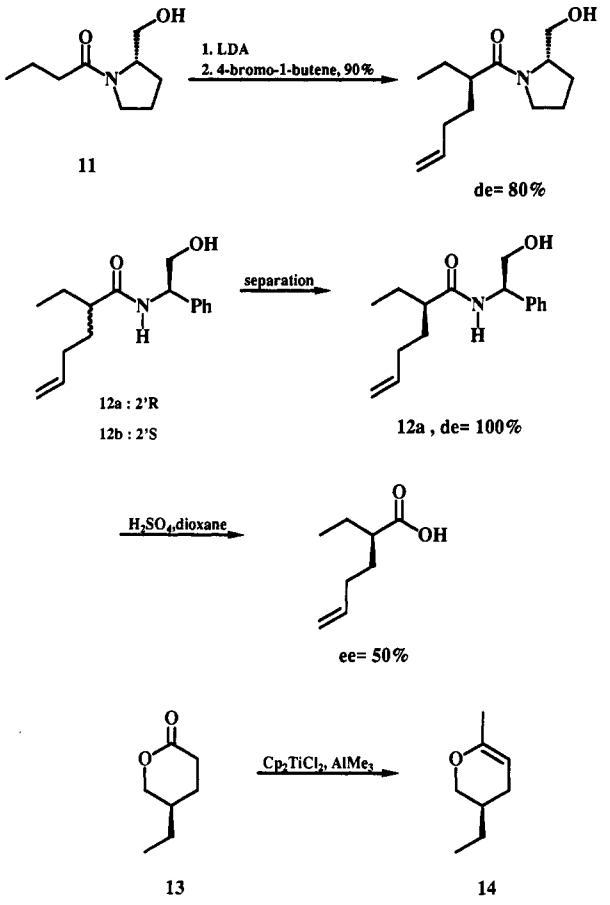
(12) Similar results using simple haloalkanes have been obtained by Evans (see ref 11).

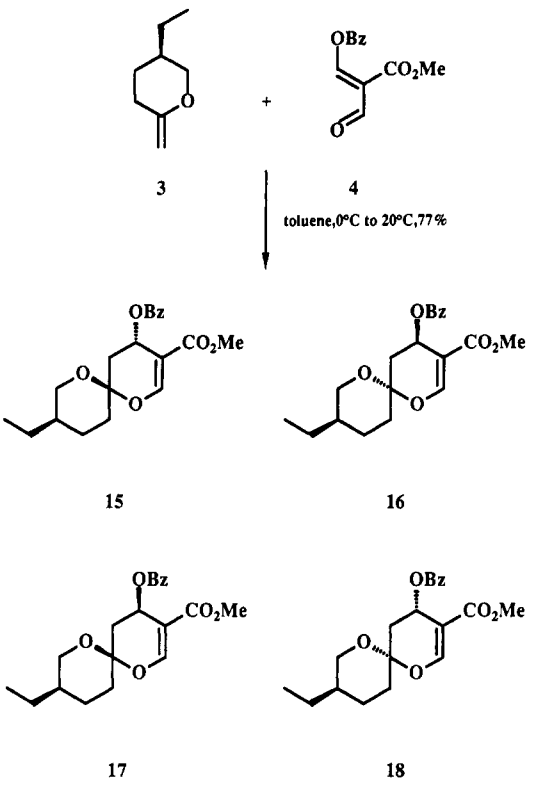
Scheme III



alkylating agent. This electrophile exhibited good reactivity (87% yield) and high diastereofacial selection (>99:1). Moreover, the alkylation product **7** could be easily transformed via **8** into alcohol **9** by a reduction–hydrogenation–protodesilylation[14] sequence. The integrity of the newly created stereogenic center in **7** during the transformation of **7** to **9** was proven via the Mosher[15] ester of **9**. Gas chromatographic and ^{13}C NMR analysis of the Mosher ester confirmed the enantiomeric purity of **9** (ee >98%).

Iodoetherification[18] of **9** produced the tetrahydropyran **10** as a 2.5:1 mixture of trans and cis isomers in almost quantitative yield. Since the newly formed stereogenic center in **10** is destroyed in the transformation to **3**, the low stereoselectivity in this reaction was of no concern. The elimination step to give **3** turned out, however, to be difficult. Due to the lability of the exocyclic double bond in **3** to acid-catalyzed isomerization, all glassware had to be coated with a thin film of potassium hydroxide. Eventually, the desired vinyl ether **3** could be obtained from **10** as a single isomer in 62% yield using DBU as base. Other attempts to prepare vinyl ether **3** as well as alcohol **9** failed (Scheme III). Alkylation of the prolinol amide **11**[16] with 4-bromo-1-butene proceeded in high yield, but gave only an inseparable 9:1 mixture of diastereomeric alkylation products. Though chromatographic separation of diastereomeric phenylglycinol amides **12a,b** according to Helmchen[17] could be easily accomplished, the subsequent hydrolysis of amide **12a** in aqueous sulfuric acid and dioxane resulted in a significant loss of stereochemistry at C-2. Finally, we also tried to synthesize **3** by a Tebbe reaction[19] of lactone **13**, which could be prepared in an enantiomerically pure form with SAMP according to Enders.[20] However, mainly the endocyclic enol ether **14** was obtained in low yield with use of this method.

Scheme IV. Hetero Diels–Alder Reaction of 3 and 4



Vinyl ether **3** had to be immediately subjected to the cycloaddition and smoothly reacted with *O*-benzoyldiformylacetate (**4**) to furnish the four diastereomeric adducts **15–18** in a ratio of 3:1.5:2:1 and a total yield of 77% (Scheme IV). Fortunately, the major isomer **15** contained the correct (4*S*,6*R*) configuration at the two new stereogenic centers. However, flash chromatography of the cycloadducts gave a mixture of the trans adducts **15** and **16** as well as a mixture of the cis adducts **17** and **18**. Pure **15** could not be obtained at this stage of the synthesis.

Under the assumption that **4** reacts as an (*E*)-heterodiene,[21] **15** must arise by an exo-*E*-addition, anti to the ethyl group in **3**. The structural assignment of the cycloadducts by ^1H NMR spectroscopy relied mainly on analysis of the H-4 signal. In **15** and **16**, H-4 resonates at δ 6.07 and 6.05, respectively, as a doublet of doublet with J = 5.5 and J = 5.0 Hz. These almost equal coupling constants may indicate a fast equilibrium between the two half-chair conformations A and B, the former favored by the anomeric effect[22] and the latter by the pseudoaxial

(13) 1-Bromo-4-(trimethylsilyl)-2-butyne was synthesized by bromination of the corresponding alcohol with PBr_3. See also: Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1988**, *44*, 6729.
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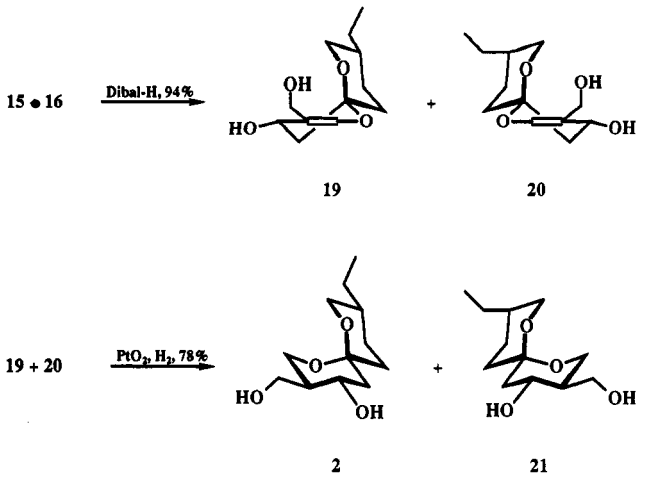
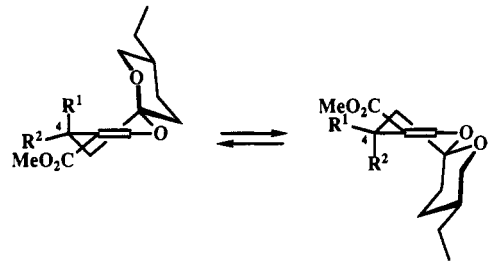
(22) Deslongchamps, P. *Stereoelectronic Effects in Organic Synthesis*; Pergamon Press: Oxford, 1983.

Scheme V. Synthesis of Talaromycin B (2) from 15



position of the OBz group at C-4 (conformations shown for **15** and **17** only).



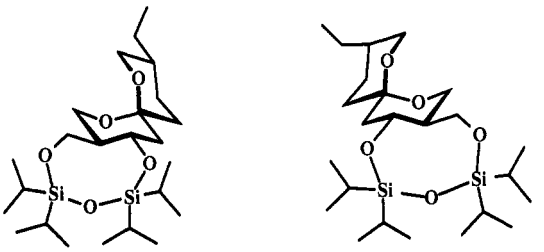
	R^1	R^2
15	H	OBz
17	OBz	H

Thus, it has been shown for many related 3-substituted dihydropyrans that electron-withdrawing groups at C-4 strongly prefer a pseudoaxial orientation (vinylogous anomeric effect).[23] Therefore, the 4,6-relationship in **15** and **16** must be trans. In **17** and **18** the signals for H-4 are found at δ 5.92 and 5.91, respectively, as doublets of doublets with J = 5.2 and J = 1.5 Hz. From the coupling constants it can be deduced that **17** and **18** only exist in conformation A with a 4,6-cis relationship. This assumption is supported by the fact that both the anomeric effect and the pseudoaxial orientation of the OBz group at C-4 should favor this conformation. The structural distinction between **15** and **16** could only be achieved by correlation with the final products of the synthesis.

DIBAL-H reduction of **15** and **16** produced the acid-labile diols **19** and **20** in almost quantitative yield (Scheme V). Purification must be done carefully, since traces of acid led to the formation of significant amounts of the corresponding elimination products. Finally, hydrogenation of the double bond in **19** and **20** by employing 1160 psi of hydrogen pressure and a platinum catalyst afforded (-)-talaromycin B (**2**) together with a small amount of the diastereomer **21**. The hydrogenation is highly stereoselective, occurring only from the bottom side of **19** and **20** to give exclusively **2** from **19** and, in addition, **21** from **20**. We assume that the selectivity is due simply to steric shielding of the upper face of the double bond by the tetrahydropyran ring, though a hydrogenation controlled by a stereoelectronic effect[22] would also explain the results.

Again, separation of the two isomers **2** and **21** was not possible. However, bis-silylation of the mixture of **2** and **21** with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TIPSCl)[24] produced two cyclic silyl ethers **22** and **23**, which could be separated by column chromatography.

Treatment of **22** with tetra-*n*-butylammonium fluoride in THF yielded enantiomerically pure (-)-talaromycin B (**2**). The 500-MHz NMR spectrum of the synthetic material was identical in every detail with the published data for natural (-)-talaromycin B.[2]



Experimental Section

Instrumentation. Multiplicities of ^{13}C NMR peaks were determined with the APT pulse sequence. Mass spectra were measured at 70 eV. UV-vis spectra (λ_{max}, nm (log ϵ)) were taken in CH_3CN. IR spectra were recorded as KBr pellets or as films. Melting points are corrected.

Materials. All solvents were appropriately dried and distilled prior to use. All reactions were performed in flame-dried flasks under a positive pressure of nitrogen and monitored by TLC (Machery, Nagel & Co. SIL G/UV_{254}). Flash chromatography was carried out on SiO_2 (Silica Woelm 32-63 active, Fa. Woelm Pharma, Eschwege).

(2′*R*,4*S*)-3-[2′-Ethyl-6′-(trimethylsilyl)-4′-hexynoyl]-4-(1-methylethyl)-2-oxazolidinone (7). A 1.6 M solution of *n*-butyllithium in hexane (6.56 mL, 10.5 mmol) was added to a solution of 1.54 mL (11.0 mmol) of diisopropylamine in 30 mL of THF at 0 °C. After being stirred for 20 min at 0 °C, the solution was cooled to -78 °C and 1.99 g (10.0 mmol) of oxazolidinone **5**[5f] was added. Stirring was continued for 1 h at -78 °C, and a solution of 3.08 g (15.0 mmol) of propargyl bromide **6**[13] in 5 mL of THF was slowly added. The reaction was kept at -78 °C for 4 h and warmed to room temperature over 8 h. The reaction was quenched with excess aqueous ammonium chloride solution, the layers were separated, and the aqueous phase was extracted three times with ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Gas chromatographic analysis of the crude mixture of alkylation products (50 m CP Sil19CB, 240 °C, 29 psi of hydrogen, t_r(minor) 6.00 min, t_r(major) 6.17 min) revealed a 99.2:0.8 diastereomeric ratio. Purification was performed by column chromatography (ethyl acetate/petroleum ether, 1:6) and afforded 2.81 g (87%) of the title compound as a colorless oil: R_f 0.44 (ethyl acetate/petroleum ether, 1:5); $[\alpha]^{20}_D$ +61.0° (*c* 1.99, $CHCl_3$); IR (film, cm^{-1}) 2234, 2204, 1780, 1700, 1388, 1204, 852; UV 205 (4.02); ^1H NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 9 H, $SiMe_3$), 0.89 (d, J = 7.0 Hz, 3 H, isopropyl-CH_3), 0.91 (t, J = 7.5 Hz, 3 H, CH_3), 0.92 (d, J = 7.0 Hz, 3 H, isopropyl-CH_3), 1.38 (t, J = 3.0 Hz, 2 H, 6′-H_2), 1.47-1.86 (m, 2 H, CH_2-CH_3), 2.38 (dsept, J = 3.8, 7.0 Hz, 1 H, isopropyl-CH), 2.51 (dt, J = 6.5, 3.0 Hz, 2 H, 3′-H_2), 3.83 (tt, J = 6.5, 6.5 Hz, 1 H, 2′-H), 4.22 (dd, J = 7.8, 3.8 Hz, 1 H, 5-H), 4.27 (dd, J = 7.8, 7.8 Hz, 1 H, 5-H), 4.49 (ddd, J = 7.8, 3.8, 3.8 Hz, 1 H, 4-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ -2.33 ($SiMe_3$), 6.76 (C-6′), 11.08 (CH_3), 14.42, 17.68 (isopropyl-CH_3), 21.32 (CH_2CH_3), 23.57 (C-3′), 28.23 (isopropyl-CH), 43.88 (C-2′), 58.22 (C-4), 62.96 (C-5), 74.85 (C-5′), 79.02 (C-4′), 153.5 (C-2), 174.5 (C-1′); MS m/z 323 (7, M^+), 202 (100), 194 (35, acyl chain - 1), 73 (89, $SiMe_3$). Anal. Calcd for $C_{17}H_{29}NO_3Si$: C, 63.12; H, 9.04. Found: C, 63.02; H, 9.17.

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(24) Markiewicz, W. T. *J. Chem. Res., Synop.* **1979**, 24.

(2*R*)-2-Ethyl-6-(trimethylsilyl)-4-hexyn-1-ol (8). Oxazolidinone **7** (2.59 g, 8.00 mmol) was added to a suspension of 304 mg (8.00 mmol) of $LiAlH_4$ in 15 mL of THF at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and quenched with 1 mL of saturated sodium bicarbonate solution and approximately 1 mL of aqueous 10% sodium hydroxide solution. The resulting mixture was filtered, diluted with ether, washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvents the residue was subjected to column chromatography (ether/petroleum ether, 1:3) to yield 1.35 g (85%) of the title compound as a colorless oil: R_f 0.57 (ether/petroleum ether, 1:1); $[\alpha]^{20}_D$ −3.1° (*c* 0.84 $CHCl_3$); IR (film, cm^{-1}) 3354, 2218, 1248, 1044, 850; ^1H NMR (200 MHz, $CDCl_3$) δ 0.09 (s, 9 H, $SiMe_3$), 0.92 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.29–1.62 (m, 3 H, 2-H, CH_2CH_3), 1.42 (t, *J* = 2.7 Hz, 2 H, 6-H_2), 1.62 (br s, 1 H, OH), 2.17 (ddt, *J* = 16.7, 6.2, 2.7 Hz, 1 H, 3-H), 2.30 (ddt, *J* = 16.7, 5.5, 2.7 Hz, 1 H, 3-H), 3.59 (dd, *J* = 11.0, 6.2 Hz, 1 H, 1-H), 3.66 (dd, *J* = 11.0, 5.0 Hz, 1 H, 1-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −2.03 ($SiMe_3$), 6.99 (C-6), 11.42 (CH_3), 20.47 (CH_2CH_3), 23.12 (C-3), 41.84 (C-2), 65.53 (C-1), 76.38 (C-5), 79.12 (C-4); MS *m/z* 198 (1, M^+), 126 (13, $M^+ - SiMe_3$), 73 (100, $SiMe_3$). Anal. Calcd for $C_{11}H_{22}OSi$: C, 66.60; H, 11.18. Found: C, 66.59; H, 11.23.

(2*R*)-2-Ethyl-5-hexen-1-ol (9). A solution of 1.19 g (6.00 mmol) of alcohol **8** and 10 mL of ethanol was added to a suspension of 500 mg of Lindlar catalyst and 5 mL of ethanol, and the mixture was hydrogenated for 12 h. The reaction mixture was filtered through Celite and evaporated in vacuo. The crude allylsilane was taken up in 30 mL of methylene chloride and cooled to 0 °C, and 2.30 mL (30.0 mmol) of trifluoroacetic acid was added. After being stirred for 30 min at 0 °C, the reaction mixture was carefully poured into excess aqueous sodium bicarbonate solution. The layers were separated, and the aqueous phase was extracted twice with ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Short-path distillation of the crude product yielded 512 mg (67%) of the desired alcohol as a colorless oil: bp 110 °C (oven temperature, 15 mmHg); R_f 0.27 (ether/petroleum ether, 1:3); $[\alpha]^{20}_D$ −4.7° (*c* 1.05, $CHCl_3$); IR (film, cm^{-1}) 3332, 1642, 1046; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.28–1.56 (m, 6 H, 2-H, 3-H_2, CH_2CH_3, OH), 2.09 (mc, 2 H, 4-H_2), 3.58 (d, *J* = 6.0 Hz, 2 H, 1-H_2), 4.95 (ddt, *J* = 10.5, 2.0, 1.0 Hz, 1 H, 6-H), 5.02 (ddt, *J* = 17.0, 2.0, 2.0 Hz, 1 H, 6-H), 5.82 (ddt, *J* = 17.0, 10.5, 6.5, Hz, 1 H, 5-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.07 (CH_3), 23.30 (CH_2CH_3), 29.72 (C-3), 31.16 (C-4), 41.44 (C-2), 65.00 (C-1), 114.4 (C-6), 139.1 (C-5); MS *m/z* 128 (4, M^+), 110 (12, $M^+ - H_2O$), 81 (54, $M^+ - 1 - CH_2OH - CH_3$). Anal. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 75.03; H, 12.62.

(2*RS*,5*R*)-2-(Iodomethyl)-5-ethyltetrahydropyran (10). Alcohol **9** (487 mg, 3.80 mmol) was added to a suspension of 1.45 g (5.71 mmol) of iodine and 0.48 g (5.71 mmol) of sodium bicarbonate in 10 mL of ether and 3 mL of water at 0 °C. The mixture was stirred at room temperature for 8 h and washed with excess aqueous sodium thiosulfate solution. The layers were separated, and the aqueous phase was extracted twice with ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was filtered through a plug of silica gel (ether/petroleum ether, 1:10) to afford 888 mg (92%) of the title compound as a slightly pink oil. ^{13}C NMR analysis revealed a 2.5:1 mixture of trans and cis isomers: R_f 0.75 (ether/petroleum ether, 1:10); $[\alpha]^{20}_D$ +9.2° (*c* 1.62, $CHCl_3$); IR (film, cm^{-1}) 1460, 1174, 1084; UV 194 (3.83), 252 (2.75); ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3 H, CH_3, major isomer), 0.92 (t, *J* = 7.0 Hz, 3 H, CH_3, minor isomer), 1.06–2.00 (m, 7 H, 3-H_2, 4-H_2, 5-H, CH_2CH_3), 3.08 (dd, *J* = 11.0, 11.0 Hz, 1 H, 6-H_{ax}, major isomer), 3.16–3.50 (m, 3 H, $CHCH_2I$), 3.61 (dd, *J* = 11.0, 3.0 Hz, 1 H, 6-H_{ax}, minor isomer), 3.84 (dm, *J* = 11.0 Hz, 1 H, 6-H_{eq}, minor isomer), 4.02 (ddd, *J* = 11.0, 4.5, 2.0 Hz, 1 H, 6-H_{eq}, major isomer); ^{13}C NMR (50 MHz, $CDCl_3$) (major isomer) δ 9.93 (CH_2CH_3), 11.21 (CH_3), 24.93, 29.63, 31.65, (C-3, C-4, CH_2I), 37.12 (C-5), 73.70 (C-6), 76.91 (C-2), (minor isomer) δ 9.87 (CH_2CH_3), 12.11 (CH_3), 22.93, 26.59, 27.04 (C-3, C-4, CH_2I), 35.17 (C-5), 70.72 (C-6), 76.76 (C-2); MS *m/z* 254 (19, M^+), 226 (18, $M^+ + 1$ − ethyl), 127 (9, $M^+ - I$), 113 (100, $M^+ - CH_2I$). Anal. Calcd for $C_8H_{15}OI$: C, 37.81; H, 5.95. Found: C, 37.93; H, 6.05.

(5*R*)-5-Ethyl-2-methylenetetrahydropyran (3). For the preparation of the title compound all glassware that was subjected to elevated temperatures (reaction, evaporation, and distillation) was washed with a concentrated solution of potassium hydroxide in a water/ethanol mixture (1:1) and dried at 150 °C in an oven. Tetrahydropyran **10** (864 mg, 3.40 mmol) and 0.81 mL (5.42 mmol) of DBU were heated at 90 °C for 30 min. The mixture was diluted with ether, washed with water, and dried over $MgSO_4$. The ether was distilled at a bath temperature of 60–70 °C and atmospheric pressure. Short-path distillation of the residue afforded 266 mg (62%) of a colorless oil that was immediately used in the following reaction: bp 80–90 °C (oven temperature, 25 mmHg); $[\alpha]^{20}_D$ −111.7° (*c* 0.47, cyclohexane); ^1H NMR (200 MHz, C_6D_6) δ 0.63 (t, *J* = 7.0 Hz, 3 H, CH_3), 0.72–1.03 (m, 3 H, $CHCH_2CH_3$), 1.22–1.59 (m, 2 H, 4-H_2), 1.93–2.18 (m, 2 H, 3-H_2), 3.17 (dd, *J* = 10.5, 10.0 Hz, 1 H, 6-H_{ax}), 3.90 (ddd, *J* = 10.5, 4.0, 2.0 Hz, 1 H, 6-H_{eq}), 4.12 (d, *J* = 1.5 Hz, 1 H, (*E*)-vinyl-H) 4.64 (m, 1 H, (*Z*)-vinyl-H); ^{13}C NMR (20 MHz, C_6D_6) δ 11.24 (CH_3), 24.95 (CH_2CH_3), 28.85, 29.24 (C-3, C-4), 36.66 (C-5), 73.68 (C-6), 90.90 (H_2C=C), 160.5 (C=CH_2); MS *m/z* 126 (89, M^+), 111 (15, $M^+ - CH_3$), 97 (53, $M^+ - C_2H_5$). Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.15; H, 11.16.

Hetero Diels–Alder Reaction of 3 and *O*-Benzoyldiformylacetate (4). The dry sodium salt of methyl diformylacetate[8] (456 mg, 3.00 mmol), which was obtained by titration of the free acid with aqueous sodium hydroxide solution and drying in vacuo, was dissolved in 5.00 mL of toluene and treated with 0.35 mL (3.00 mmol) of freshly distilled benzoyl chloride. The suspension was stirred for 1 h at room temperature and cooled to 0 °C. Then a solution of the freshly prepared vinyl ether **3** (252 mg, 2.00 mmol) in 2.00 mL of toluene was added. Stirring was continued for 5 h at 0 °C and for an additional 8 h at room temperature. The mixture was poured into excess aqueous sodium bicarbonate solution, the layers were separated, and the aqueous phase was extracted three times with ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to afford a red, viscous oil that was subjected to filtration through a plug of silica gel (ether/petroleum ether, 1:2) to remove polymers and other byproducts. The crude mixture of Diels–Alder products was purified by flash chromatography (ether/petroleum ether, 1:3):

(4*S*,6*R*,9*R*)- and (4*R*,6*S*,9*R*)-4-(Benzoyloxy)-9-ethyl-3-(methoxycarbonyl)-1,7-dioxaspiro[5.5]undec-2-ene (15 and 16): 333 mg (46%); R_f 0.44 (ether/petroleum ether, 1:2); mp 87–88 °C (ether/petroleum ether); $[\alpha]^{20}_D$ +2.3° (*c* 0.95, $CHCl_3$); IR (KBr, cm^{-1}) 1712, 1628, 1276, 1224, 1106, 1092; UV 196 (4.73), 232 (4.50); ^1H NMR (200 MHz, $CDCl_3$) (for **15**) δ 0.90 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.10–1.32 (m, 2 H, CH_2CH_3), 1.40–1.79 (m, 5 H, 9-H, 10-H_2, 11-H_2), 2.14 (dd, *J* = 14.5, 5.0 Hz, 1 H, 5-H_{ax}), 2.31 (dd, *J* = 14.5, 5.5 Hz, 1 H, 5-H_{eq}), 3.55 (dd, *J* = 11.0, 11.0 Hz, 1 H, 8-H_{ax}), 3.62–3.78 (m, 1 H, 8-H_{eq}), 3.67 (s, 3 H, CO_2CH_3), 6.07 (dd, *J* = 5.5, 5.0 Hz, 1 H, 4-H), 7.38–7.60 (m, 3 H, aromatic), 7.67 (s, 1 H, 2-H), 7.96–8.04 (m, 2 H, aromatic), (different values for **16**) δ 0.92 (t, *J* = 7.0 Hz, 3 H, CH_3), 2.15 (dd, *J* = 14.5, 5.0 Hz, 1 H, 5-H_{ax}), 2.30 (dd, *J* = 14.5, 5.5 Hz, 1 H, 5-H_{eq}), 6.05 (dd, *J* = 5.5, 5.0 Hz, 1 H, 4-H); ^{13}C NMR (50 MHz, $CDCl_3$) (for **15**) δ 11.05 (CH_3), 24.49, 25.05 (C-10, CH_2CH_3), 32.43 (C-11), 36.09 (C-9), 38.08 (C-5), 51.36 (CO_2CH_3), 62.95 (C-4), 67.30 (C-8), 100.3 (C-6), 105.7 (C-3), 128.4 (C-3-aromatic), 129.6 (C-2-aromatic), 130.3 (C-1-aromatic), 132.9 (C-4-aromatic), 155.8 (C-2), 165.7, 166.5 (2 CO), (different values for **16**) δ 22.14, 22.42 (C-10, CH_2CH_3), 27.87 (C-11), 33.98 (C-9), 37.74 (C-5), 65.23 (C-8), 100.7 (C-6); diastereomeric ratio **15**:**16** = 2:1; MS *m/z* 360 (1, M^+), 238 (53, M^+ − PhCOOH), 206 (35, M^+ − PhCOOH − MeOH), 126 (100, vinyl ether **3**, retro Diels–Alder). Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.73; H, 6.70.

(4*R*,6*R*,9*R*)- and (4*S*,6*S*,9*R*)-4-(Benzoyloxy)-9-ethyl-3-(methoxycarbonyl)-1,7-dioxaspiro[5.5]undec-2-ene (17 and 18): 222 mg (31%); R_f 0.33 (ether/petroleum ether, 1:2); $[\alpha]^{20}_D$ −13.1 (*c* 0.93, $CHCl_3$); IR (film, cm^{-1}) 1712, 1618, 1272, 1218, 1106, 1092, UV 196 (4.59), 232 (4.47); ^1H NMR (200 MHz, $CDCl_3$) (for **17**) δ 0.89 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.12–1.30 (m, 2 H, CH_2CH_3), 1.40–1.90 (m, 5 H, 9-H, 10-H_2, 11-H_2), 2.02 (dd, *J* = 15.5, 5.2 Hz, 1 H, 5-H_{ax}), 2.39 (dd, *J* = 15.5, 1.5 Hz, 1 H, 5-H_{eq}), 3.43 (dd, *J* = 11.0, 11.0 Hz, 1 H, 8-H_{ax}), 3.63–3.75 (m, 1 H, 8-H_{eq}), 3.68 (s, 3 H, CO_2CH_3), 5.92 (dd, *J* = 5.2, 1.5 Hz, 1 H, 4-H), 7.36–7.58 (m, 3 H, aromatic), 7.74 (s, 1 H, 2-H), 7.99–8.06 (m, 2 H, aromatic), (different values for **18**) δ 0.87 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.86 (dd,

J = 15.5, 5.2 Hz, 1 H, 5-H_{ax}), 2.50 (dd, J = 15.5, 1.5 Hz, 1 H, 5-H_{eq}), 5.91 (dd, J = 5.2, 1.5 Hz, 1 H, 4-H); ^{13}C NMR (50 MHz, $CDCl_3$) (for **17**) δ 11.01 (CH_3), 24.37, 25.06 (C-10, CH_2CH_3), 34.08 (C-11), 35.94 (C-9), 37.21 (C-5), 51.33 (CO_2CH_3), 60.92 (C-4), 67.05 (C-8), 97.57 (C-6), 105.8 (C-3), 128.1 (C-3-aromatic), 129.7 (C-2-aromatic), 130.8 (C-1-aromatic), 132.6 (C-4-aromatic), 155.8 (C-2), 166.2, 166.6 (2 CO), (different values for **18**) δ 22.50, 22.69 (C-10, CH_2CH_3), 30.07 (C-11), 34.20 (C-9), 36.03 (C-5), 60.99 (C-4), 65.48 (C-8), 98.21 (C-6), 156.0 (C-2); diastereomeric ratio **17**:**18** = 2:1, MS m/z 360 (1, M^+), 255 (40, M^+ − benzoyl), 238 (56, M^+ − PhCOOH), 206 (37, M^+ − PhCOOH − MeOH), 126 (100, vinyl ether **3**, retro Diels–Alder). Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.77; H, 6.72.

(4*S*,6*R*,9*R*)- and (4*R*,6*S*,9*R*)-9-Ethyl-4-hydroxy-3-(hydroxymethyl)-1,7-dioxaspiro[5.5]undec-2-ene (19 and 20). A solution of 324 mg (0.90 mmol) of **15** and **16** in 10.0 mL of THF was treated with 6.00 mL (6.00 mmol) of a 1 M Dibal-H solution in toluene at −78 °C. The solution was stirred and warmed to room temperature overnight and quenched with 0.20 mL of an aqueous sodium bicarbonate solution and approximately 0.30 mL of an aqueous 10% sodium hydroxide solution. The resulting mixture was filtered, diluted with ether, washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvents the residue was subjected to column chromatography (ethyl acetate/petroleum ether/methanol, 5:4:1) and yielded 192 mg (94%) of the title compounds as a colorless oil: R_f 0.57 (ethyl acetate/petroleum ether/methanol, 5:4:1); $[\alpha]^{20}_D$ −61.8° (*c* 0.60, $CHCl_3$); IR (film, cm^{-1}) 3384, 1668, 1166, 1078, 1032, 986; UV 205 (3.94); ^{1}H NMR (200 MHz, C_6D_6) (for **19**) δ 0.70 (t, J = 7.0 Hz, 3 H, CH_3), 0.84–1.16 (m, 2 H, CH_2CH_3), 1.20–2.06 (m, 5 H, 9-H, 10-H_2, 11-H_2), 1.34 (dd, J = 13.0, 7.0 Hz, 1 H, 5-H_{ax}), 2.21 (dd, J = 13.0, 6.5 Hz, 1 H, 5-H_{eq}), 2.40–2.80 (br s, 1 H, OH), 3.20–3.50 (br s, 1 H, OH), 3.41 (dd, J = 11.0, 11.0 Hz, 1 H, 8-H_{ax}), 3.58 (dd, J = 11.0, 4.0 Hz, 1 H, 8-H_{eq}), 4.03 (br d, J = 13.5 Hz, 1 H, CH_2OH), 4.10 (br d, J = 13.5 Hz, 1 H, CH_2OH), 4.78 (m, 1 H, 4-H), 6.20 (br s, 1 H, 2-H), (observed different values for **20**) δ 0.77 (t, J = 7.0 Hz, 3 H, CH_3), 3.88 (dd, J = 11.0, 3.0 Hz, 1 H, 8-H_{eq}); ^{13}C NMR (50 MHz, $CDCl_3$) (for **19**) δ 10.50 (CH_3), 23.75, 24.53 (C-10, CH_2CH_3), 33.55 (C-11), 35.95 (C-9), 40.53 (C-5), 61.37 (C-12), 62.18 (C-4), 65.90 (C-8), 97.86 (C-6), 114.5 (C-3), 139.3 (C-2), (different values for **20**) δ 11.51 (CH_3), 21.59, 22.09 (C-10, CH_2CH_3), 29.16 (C-11), 33.83 (C-9), 39.83 (C-5), 62.03 (C-4), 64.03 (C-8), 98.40 (C-6); MS m/z 228 (2, M^+), 210 (5, $M^+ - H_2O$), 192 (7, $M^+ - 2\ H_2O$), 126 (100, vinyl ether **3**, retro Diels–Alder). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.35; H, 9.04.

(3*S*,4*S*,6*R*,9*R*)-9-Ethyl-4-hydroxy-3-(hydroxymethyl)-1,7-dioxaspiro[5.5]undecane ((−)-Talaromycin B) (2). A solution of 192 mg (0.84 mmol) of the mixture of **19** and **20** in 20 mL of methanol containing 80.0 mg (0.30 mmol) of PtO_2 was subjected to a hydrogen pressure of 1160 psi at room temperature for 15 h. The catalyst was removed by filtration, the solvent was evaporated, and the residue was filtered through a short column of silica gel (ethyl acetate/petroleum ether/methanol, 2:6:0.5). The resulting mixture of talaromycins **2** and **21** (151 mg, 78%) was dissolved in 5.00 mL of pyridine and treated with 0.31 mL (1.00 mmol) of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane for 6 h at 0 °C. The pyridine was evaporated, and the residue was taken up in ether. The pyridinium hydrochloride was filtered off and the ether was evaporated. The mixture of silyl ethers was separated by column chromatography (ether/petroleum ether, 1:25): fraction 1, 176 mg of **22**, R_f 0.43 (ether/petroleum ether, 1:10); fraction 2, 83 mg of **23**, R_f 0.38 (ether/petroleum ether, 1:10).

The first eluted fraction (176 mg, 0.37 mmol of **22**) was dissolved in 5.00 mL of THF and treated with 316 mg (1.00 mmol) of tetra-*n*-butylammonium fluoride for 30 min at 0 °C. The solvent was evaporated, and the residue was purified by column chromatography (ethyl acetate/petroleum ether/methanol, 2:6:0.5) to yield 76 mg of (−)-talaromycin B (76% based on material recovered from the hydrogenation step); R_f 0.27 (ethyl acetate/petroleum ether/methanol, 2:6:0.5); mp 135–136 °C (ethyl acetate/petroleum ether); $[\alpha]^{20}_D$ −90.4° (*c* 0.51, $CHCl_3$) (lit.[5c] $[\alpha]^{24}_D$ −89.1° (*c* 0.48, $CHCl_3$); lit.[5f] $[\alpha]^{20}_D$ −84.1° (*c* 0.46, $CHCl_3$)); IR (KBr, cm^{-1}) 3384, 1378, 1186, 1084, 1074, 1048, 1038; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 3 H, CH_3), 1.16 (mc, 2 H, CH_2CH_3), 1.35–1.47 (m, 2 H, 9-H_{ax}, 10-H_{ax}), 1.45 (dd, J = 12.5, 11.0 Hz, 1 H, 5-H_{ax}), 1.54 (ddd, J = 13.0, 13.0, 4.0 Hz, 1 H, 11-H_{ax}), 1.60–1.65 (m, 1 H, 10-H_{eq}), 1.71 (ddd, J = 13.0, 3.5, 2.5 Hz, 1 H, 11-H_{eq}), 1.85 (mc, 1 H, 3-H_{ax}), 1.99 (dd, J = 12.5, 5.0 Hz, 1 H, 5-H_{eq}), 2.52 (br s, 2 H, OH), 3.20 (dd, J = 11.0, 11.0 Hz, 1 H, 8-H_{ax}), 3.31 (dd, J = 11.5, 11.5 Hz, 1 H, 2-H_{ax}), 3.52 (ddd, J = 11.0, 4.5, 2.5 Hz, 1 H, 8-H_{eq}), 3.59 (dd, J = 11.5, 5.0 Hz, 1 H, 2-H_{eq}), 3.72 (br d, J = 7.0 Hz, 2 H, 12-H_2), 4.06 (ddd, J = 11.0, 10.0, 5.0 Hz, 1 H, 4-H_{ax}); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 11.16 (CH_3), 24.76, 25.18 (C-10, CH_2CH_3), 35.16 (C-11), 36.68 (C-9), 44.09 (C-5), 45.31 (C-3), 60.21, 63.31, 65.27 (C-2, C-8, C-12), 68.43 (C-4), 97.13 (C-6); MS m/z 230 (5, M^+), 200 (3, $M^+ + 1 - CH_2OH$), 157 (5), 155 (8), 148 (6), 147 (100, $M^+ - C_6H_{11}$), 144 (55), 129 (68, $M^+ - C_6H_{13}O$), 126 56, vinyl ether **3**, retro Diels–Alder). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.57; H, 9.66.

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