JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

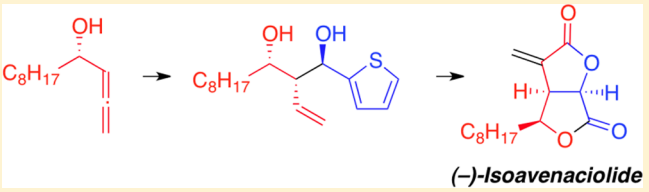
Total Synthesis of (−)-Isoavenaciolide

David Santos, Xavier Ariza,* Jordi Garcia,* Paul Lloyd-Williams, Agustín Martínez-Laporta, and Carolina Sánchez

Departament de Química Orgànica and Institut de Biomedicina de la Universitat de Barcelona (IBUB), Facultat de Química, Universitat de Barcelona, Martí i Franquès 1, 08028-Barcelona, Spain

Supporting Information

ABSTRACT: An enantioselective approach to (−)-isoavenaciolide was achieved starting from 1-undecyn-3-ol. The synthesis relied upon the preparation of a chiral 4-silyloxy-2-alkenylborane by hydroboration of a protected 2,3-allenol and subsequent stereoselective addition to 2-thiophenecarboxaldehyde.



INTRODUCTION

Isoavenaciolide ((−)-**1**) is a member of a distinct family of α-methylenebis(butyrolactone) natural products isolated from the fermentation broth of *Aspergillus* and *Penicillium* species.[1] This secondary metabolite displays a broad spectrum of antibacterial and antifungal properties and inhibits vaccinia H1-related (VHR) phosphatase activity (Figure 1).[2]

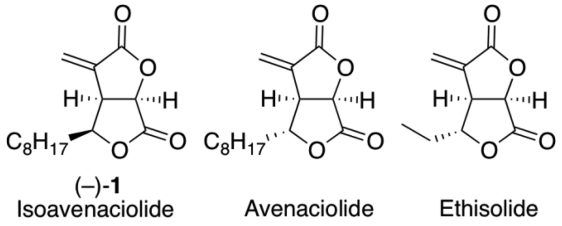
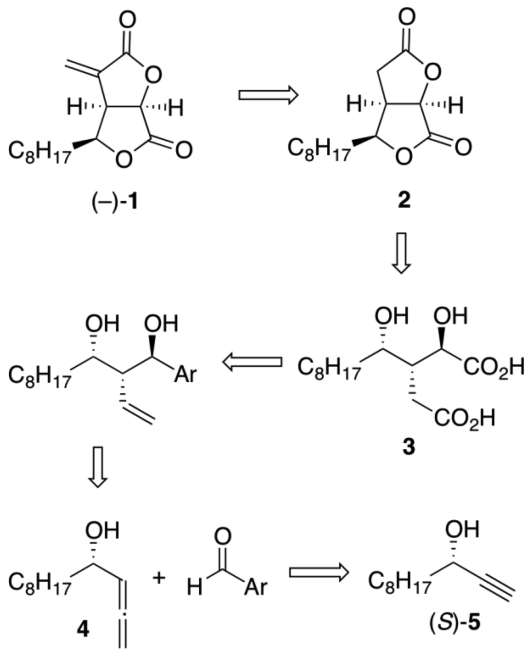


Figure 1. Isoavenaciolide and other related natural α-methylenebislactones.

On account of its biological activity and its interesting bislactone skeleton, numerous enantioselective syntheses have been reported.[3] Most of the initial approaches relied either on the transformation of chiral natural products[4] or on the Sharpless epoxidation.[5] Only recently have other stereoselective methods been used to synthesize this molecule.[6] In our search for new approaches to the preparation of polyhydroxylated frameworks, we have developed a stereoselective method for the preparation of 1,3-diols based on a tandem process that involves hydroboration of a chiral-protected 2,3-allenol followed by addition of an aldehyde.[7] We anticipated that this methodology could be applied to the synthesis of (−)-isoavenaciolide as a representative example of this family of compounds. In our retrosynthetic analysis of (−)-**1**, the methylene group would be introduced in the last step from bislactone **2** that would arise from dihydroxy diacid **3**. Such a structure could be prepared by a double oxidation of a homoallylic diol that can be synthesized stereoselectively with our methodology (Scheme 1).[8]

Scheme 1. Retrosynthetic Analysis of (−)-1



RESULTS AND DISCUSSION

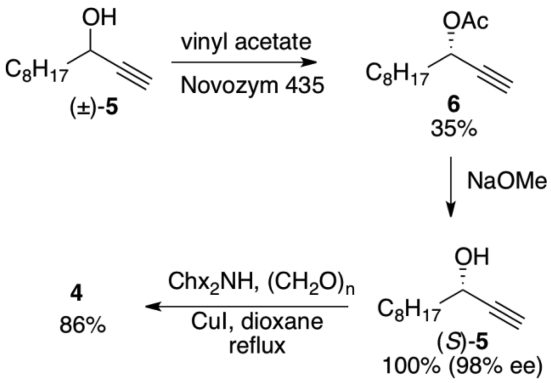
The synthesis was initiated by preparation of the enantioenriched allenol **4**. 2,3-Allenols can be easily obtained from the corresponding propargylic alcohols by a Cu(I)-mediated homologation process with paraformaldehyde.[9] Among the variety of methods available for the synthesis of enantiopure 1-alkyn-3-ols, such as (*S*)-**5**, we preferred to employ one based on enzymatic resolution.[10] Thus, kinetic resolution of 1-undecyn-3-ol (±)-(**5**) with Novozym 435 (*Candida antarctica* lipase)

Received: November 29, 2012
Published: January 21, 2013

   dx.doi.org/10.1021/jo302598h | *J. Org. Chem.* 2013, 78, 1519−1524

and vinyl acetate afforded enantioenriched (*S*)-**5** as acetate **6** that was hydrolyzed and homologated to allenol **4** under the conditions described above (Scheme 2).[11]

Scheme 2. Preparation of Enantioenriched Allenol 4



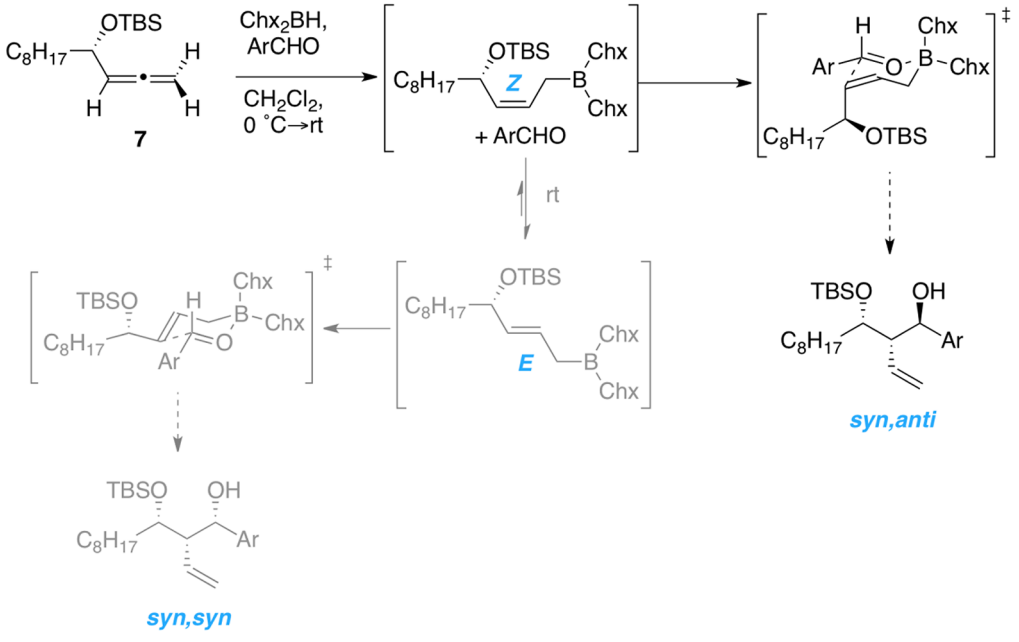
Our recently described methodology of addition of protected 2,3-allenols to aldehydes is based on the hydroboration of an allene and the addition of the transient 2-alkenylborane to an aldehyde (Scheme 3). Initially, the borane adds to the sterically less hindered face of the allene to form a (*Z*)-2-alkenylborane. The addition of an aromatic aldehyde to this then affords a *syn,anti* homoallylic alcohol through a six-membered transition state. The *anti* relationship between the vinyl and hydroxyl groups arises from the stereochemistry of the olefin (*Z*), whereas the *syn* relationship of the vinyl and the silyloxy groups derives from the face of the aldehyde that is added to the chiral 2-alkenylborane. An important feature of our method is that the kinetically formed (*Z*)-borane isomerizes to the thermodynamically more stable (*E*)-2-alkenylborane at room temperature, such that when the aldehyde is not added immediately, isomerization can occur and the *syn,syn* stereoisomer is obtained as the major product. Consequently, the *syn,anti* stereoisomer is only obtained as the major isomer when an aromatic aldehyde is employed and the (*Z*)-borane is trapped before isomerization.

In the present case, since the required stereochemistry was *syn,anti* (Scheme 2), an aromatic aldehyde was required in order to ensure high stereoselectivities.[12] Among the different possibilities, we chose 2-thiophenecarboxaldehyde on account of its being easier to oxidize at a later stage in the synthesis. In previous studies,[7] we have shown that the TBS group is a very convenient option for the protection of **4** in these additions, whereas other silicon-based protecting groups such as TBDPS lowered the stereoselectivity of the addition. Thus, allene **7** was prepared by protection of allenol **4** with TBS-chloride (Scheme 4), and its addition to 2-thiophenecarboxaldehyde gave a diastereomeric mixture (dr 84:16) of *syn,anti*-**8** and *syn,syn*-**8**. The expected major isomer *syn,anti*-**8** was isolated in 80% yield.[13]

The oxidation of the terminal olefin in *syn,anti*-**8** to a carboxylic acid was planned to take place in two steps: initial regioselective oxidation of the vinyl group to the primary alcohol followed by concomitant oxidation[14] and the thiophene with $NaIO_4/RuCl_3$ which would afford dicarboxylic acid **3**.

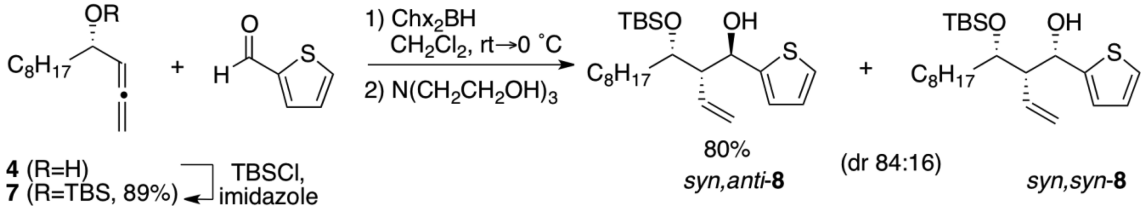
An expeditious method for achieving this turned out to be protection of both oxygens of *syn,anti*-**8** as acetyl groups (Scheme 5). Thus, deprotection of the TBS group of **8** afforded diol **9**, and its acetylation gave diacetylated olefin **10**. This was then hydroborated with dicyclohexylborane, and the resulting borane was oxidized at neutral pH to afford **11**. Simultaneous oxidation of the alcohol and the thiophene moiety then afforded dicarboxylic acid **12** in good yield. Nevertheless, hydroboration/oxidation of *syn,anti*-**8** did require care in its execution. Basic oxidations of the borane intermediate (with $H_2O_2/NaOH$) promoted the migration of an acetyl group to the primary alcohol of **11**, and crude **11** required immediate purification in order to avoid its decomposition. Protective group migration could not be avoided by switching to temporary silicon-based groups such as TBS or TBDPS nor by using other hydroborating systems such as $BH_3{:}SMe_2$ or

Scheme 3. Addition of Protected 2,3-Allenols to Aldehydes

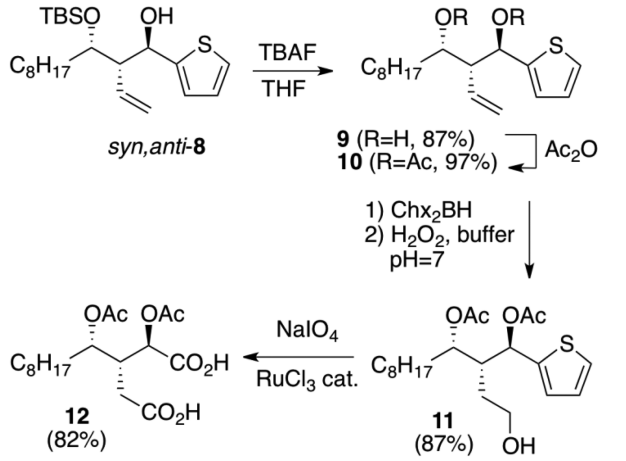


dx.doi.org/10.1021/jo302598h | *J. Org. Chem.* 2013, 78, 1519−1524

Scheme 4. Addition of Allene 7 to 2-Thiophenecarboxaldehyde



Scheme 5. Synthesis of Dicarboxylic Acid 12



catecholborane/Rh (Table 1). Yields of **11** were also not improved using these reagents.

Table 1. Hydroboration of 10

entry	hydroborating agent	oxidant	yield (%)
1	catecholborane/$RhCl(PPh_3)_3$	H_2O_2/NaOH	0
2	catecholborane/$RhCl(PPh_3)_3$	H_2O_2/buffer pH = 7	40
3	BH_3:SMe_2	H_2O_2/buffer pH = 7	0
4	BH_3:SMe_2	H_2O_2/NaOH	26
5	Chx_2BH	H_2O_2/buffer pH = 7	87

The final steps of the synthesis were quite straightforward. Hydrolysis of crude diacetate **12** afforded dihydroxy diacid **3** that cyclized in situ, giving bislactone **2**. Methylenation was easily achieved by a known procedure[15] that completed the total synthesis of (−)-isoavenaciolide (Scheme 6). The optical rotation of the synthetic product was in good agreement with the value reported in the literature.[5d]

CONCLUSIONS

The enantioselective synthesis of (−)-isoavenaciolide (**1**) described here constitutes a direct application of our recent stereodivergent approach to 2-vinyl-1,3-diols based on a tandem allene hydroboration/aldehyde addition process to natural product synthesis. This approach takes advantage of the good facial discrimination of aromatic aldehydes by the transient chiral (*Z*)-2-alkenylborane formed from a chiral allene. Temporary protection of 1,3-diol **9** as its diacetate **10** very conveniently facilitated the oxidation steps that led to diacid **12** that then cyclized to bislactone **2**.

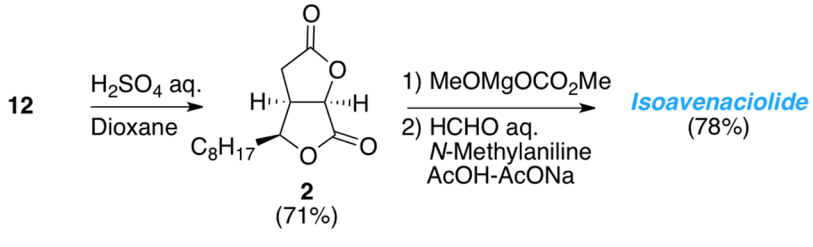
EXPERIMENTAL SECTION

All reactions involving moisture- or air-sensitive reagents were performed in oven-dried glassware under N_2. Chemical shifts (δ) are quoted in parts per million and referenced to internal TMS for ^1H NMR and to $CDCl_3$ (δ 77.0 ppm) or CD_3OD (δ 49.0 ppm) for ^{13}C NMR. Column chromatography was performed on silica gel (Merck 230-400 mesh). HRMS analyses were recorded on a LC/MSD-TOF mass spectrometer.

(±)-Undec-1-yn-3-ol ((±)-5). *n*-Butyllithium (2.5 M in hexanes, 13.2 mL, 33 mmol) was added to a solution of ethynyltrimethylsilane (4.57 mL, 33 mmol) in anhydrous THF under N_2 at −40 °C. The mixture was stirred for 10 min, and nonanal (5.15 mL, 30 mmol) was added dropwise at −40 °C. After 10 min, the reaction was allowed to warm to rt and then stirred for 45 min. The reaction was quenched with H_2O (20 mL) and K_2CO_3 (2.5 g) and stirred for 2 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the organic layer was dried over $MgSO_4$, and solvents were removed. Flash chromatography (silica gel, hexanes/AcOEt 98:2) gave (±)-**5** as a colorless oil (4.64 g, 27.6 mmol, 92%): R_f (hexanes/AcOEt 8:2) 0.58; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (3H, t, J = 6.8 Hz), 1.25−1.35 (10H, m), 1.40−1.50 (2H, m), 1.67−1.75 (2H, m), 1.80 (1H, br s), 2.45 (1H, d, J = 3.0 Hz), 4.36 (1H, td, J = 6.4, 3.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.6, 25.0, 29.2, 29.2, 29.5, 31.8, 37.7, 62.3, 72.8, 85.0; IR (film, cm^{-1}) 3406, 3302, 2928, 2157, 1098; HRMS (ESI +) calcd for $C_{11}H_{21}O$ $(M + H)^+$ 169.1587, found 169.1592.

(*S*)-Undec-1-yn-3-yl acetate (6). Racemic alcohol (±)-**5** (4.64 g, 27.6 mmol) was treated with vinyl acetate (30 mL) in the presence of Novozym 435 (0.250 g). The mixture was stirred under N_2, until ^1H NMR showed 40% conversion. The mixture was filtered and the solvent removed. The crude product was purified by flash chromatography (silica gel, hexanes/AcOEt 9:1) to give **5** (2.704 g, 16.1 mmol, 58%) and (−)-**6** (2.05 g, 9.8 mmol, 35%) as a colorless oil: R_f (hexanes/AcOEt 8:2) 0.83; $[\alpha]_D^{25}$ −58.6 (*c* 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (3H, t, J = 6.8 Hz), 1.25−1.35 (10H, m), 1.39−1.48 (2H, m), 1.73−1.80 (2H, m), 2.09 (3H, s), 2.44 (1H, d, J = 2.2 Hz), 5.33 (1H, td, J = 6.9, 2.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 21.0, 22.6, 24.9, 29.1, 29.2, 29.4, 31.8, 34.6, 63.8, 73.3, 81.3,

Scheme 6. Final Steps toward (−)-Isoavenaciolide



dx.doi.org/10.1021/jo302598h | J. Org. Chem. 2013, 78, 1519−1524

169.9; IR (film, cm^{-1}) 3311, 2924, 2166, 1740, 1226; HRMS (ESI+) calcd for $C_{13}H_{22}NaO_2$ $(M + Na)^+$ 233.1512, found 233.1519.

(*S*)-Undec-1-yn-3-ol ((*S*)-5). Acetate **6** (1.20 g, 5.71 mmol) was added to MeONa (1.50 g, 28 mmol) in anhydrous MeOH (20 mL), and the mixture was stirred for 2 h. The solvent was removed, and CH_2Cl_2 (10 mL) and 2 N HCl (10 mL) were added. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the organic layer was dried over $MgSO_4$, and solvents were removed to give (*S*)-**5** (0.959 g, 5.70 mmol, 100%) as a colorless oil: $[\alpha]_D^{25}$ +4.8 (*c* 0.99, $CHCl_3$).

The enantiomeric purity of alcohol **5** was determined by HPLC analysis of the corresponding benzoate (**13**) prepared by reaction of **5** with benzoyl chloride. Racemic ester was separated into two peaks of t_R 6.3 min (*R* enantiomer) and 7.3 min (*S* enantiomer) employing a column CHIRALPAK IA (0.46 cm Ø × 25 cm) with hexane. The enantiomeric excess of (*S*)-**5** was 98%.

(*S*)-Undec-1-yn-3-yl benzoate (13): Colorless oil; $[\alpha]_D^{25}$ −31.3 (*c* 0.99, $CHCl_3$); R_f (hexanes/AcOEt 8:2) 0.6; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (3H, *J* = 6.4 Hz), 1.25−1.40 (10H, m), 1.53 (2H, q, *J* = 7.6 Hz), 1.92 (2H, m), 2.48 (1H, *J* = 2.4 Hz), 5.59 (1H, td, *J* = 6.8, 2.0 Hz), 7.45 (2H, m), 7.57 (1H, m), 8.07 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.6, 24.9, 29.1, 29.2, 29.4, 31.8, 34.7, 64.4, 73.6, 81.3, 128.4, 129.8, 129.9 133.1, 165.5; IR (film, cm^{-1}) 3308, 3063, 2923, 2197, 1720, 1261; HRMS (ESI+) calcd for $C_{18}H_{25}O_2$ $(M + H)^+$ 273.1849, found 273.1844.

(*S*)-Dodeca-1,2-dien-4-ol (4). A solution of dicyclohexylamine (2.23 mL, 11.3 mmol) and (*S*)-**5** (0.95 g, 5.6 mmol) in anhydrous dioxane (20 mL) was added dropwise under N_2 to a stirred solution of paraformaldehyde (0.42 g, 14.1 mmol) and CuI (0.538 g, 2.82 mmol) in anhydrous dioxane (20 mL). The mixture was heated at reflux for 4 h. Solvent removal followed by flash chromatography (silica gel, hexanes/AcOEt 98:2) gave **4** (0.885 g, 4.8 mmol, 86%) as a yellow oil: R_f (hexanes/AcOEt 8:2) 0.5; $[\alpha]_D^{25}$ +2.6 (*c* 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86 (3H, t, *J* = 6.4 Hz), 1.25−1.48 (12H, m), 1.54−1.60 (3H, m), 4.16 (1H, m), 4.85 (2H, m), 5.24 (1H, q, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.6, 25.4, 29.2, 29.5, 29.5, 31.8, 37.5, 69.7, 77.4, 94.9, 207.0; IR (film, cm^{-1}) 3334, 2921, 1955, 1035; HRMS (ESI+) calcd for $C_{12}H_{23}O$ $(M + H)^+$ 183.1743, found 183.1742.

(*S*)-4-*tert*-Butyldimethylsilyloxydodeca-1,2-diene (7). A solution of *tert*-butyldimethylsilyl chloride (1.10 g, 7.3 mmol) in anhydrous THF (15 mL) was added dropwise under N_2 to a stirred solution of **4** (0.665g, 3.6 mmol) and imidazole (0.62 g, 9.0 mmol) at rt. The mixture was stirred for 3 h and then quenched with saturated aqueous NH_4Cl (10 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried over Mg_2SO_4. Filtration, followed by solvent removal and chromatography (silica gel, hexanes/AcOEt 98:2), gave **7** (0.962 g, 3.2 mmol, 89%) as a colorless oil: R_f (hexanes/AcOEt 95:5) 0.9; $[\alpha]_D^{25}$ −9.6 (*c* 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.05 (3H, s), 0.06 (3H, s), 0.88−0.92 (12H, m), 1.24−1.40 (12H, m), 1.47−1.57 (2H, m), 4.14 (1H, m), 4.72 (2H, m), 5.09 (1H, q, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) −4.9, −4.3, 14.1, 18.2, 22.7, 25.5, 25.9, 29.3, 29.5, 29.6, 31.9, 38.7, 71.6, 75.7, 95.0, 207.4; IR (film, cm^{-1}) 2925, 1956, 1078; HRMS (ESI+) calcd for $C_{18}H_{37}OSi$ $(M + H)^+$ 297.2608, found 297.2599.

(1*R*,2*S*,3*S*)-3-*tert*-Butyldimethylsilyloxy-1-(thiophen-2-yl)-2-vinylundecan-1-ol (*syn*,*anti*-8). A solution of **7** (0.962 g, 3.2 mmol) and 2-thiophenecarboxaldehyde (0.36 mL, 3.9 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise to a stirred suspension of dicyclohexylborane (0.807 g, 4.5 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C under N_2. After 10 min at 0 °C, the mixture was allowed to come to rt and was stirred for 4 h, until it became homogeneous. Triethanolamine (1.01 mL, 8.1 mmol) in CH_2Cl_2 (10 mL) was added, and stirring was continued for 1 h. Solvent removal followed by flash chromatography (silica gel, hexanes/AcOEt 99:1) afforded *syn*,*anti*-**8** as colorless oil (1.06 g, 2.6 mmol, 80%): R_f (hexanes/AcOEt 95:5) 0.3; $[\alpha]_D^{25}$ −4.4 (*c* 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.12 (3H, s), 0.18 (3H, s), 0.89 (3H, t, *J* = 7.2 Hz), 0.95 (9H, s), 1.25−1.35 (10H, m), 1.35−1.45 (2H, m), 1.55−1.65 (2H, m), 2.59 (1H, td, *J* = 9.0, 2.7 Hz), 3.99 (1H, ddd, *J* = 7.8, 5.6, 2.7 Hz), 4.34 (1H, d, *J* = 1.0 Hz), 4.92 (1H, ddd, *J* = 17.2, 1.6, 0.4 Hz), 5.01 (1H, dd, *J* = 10.4, 1.6 Hz), 5.09 (1H, dd, *J* = 9.0, 2.0 Hz), 5.60 (1H, ddd, *J* = 17.2, 10.4, 9.2 Hz), 6.90 (2H, m), 6.21 (1H, dd, *J* = 4.8, 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.4, −4.3, 14.1, 18.0, 22.7, 25.9, 26.1, 29.2, 29.5, 29.6, 31.8, 33.0, 56.2, 71.5, 75.5, 118.4, 124.1, 124.5, 126.1, 134.8, 148.3; IR (film, cm^{-1}) 3446, 3073, 2926, 1252; HRMS (ESI+) calcd for $C_{23}H_{42}NaO_2SSi$ $(M + Na)^+$ 433.2567, found 433.2564.

(1*R*,2*R*,3*S*)-1-(Thiophen-2-yl)-2-vinylundecane-1,3-diol (9). A solution of *syn*,*anti*-**8** (1.06 g, 2.6 mmol) and TBAF·$3H_2O$ (4.07 g, 12.9 mmol) in anhydrous THF (15 mL) under N_2 was stirred at rt for 24 h. The mixture was quenched with a saturated aqueous NH_4Cl (10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and solvent removal then gave the crude product that was purified by column chromatography (silica gel, hexanes/AcOEt 7:3), affording **9** as a colorless oil 0.642 g (2.2 mmol, 84%): R_f (hexanes/AcOEt 8:2) 0.28; $[\alpha]_D^{25}$ −3.2 (*c* 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (3H, t, *J* = 6.4 Hz), 1.23−1.35 (12H, m), 1.38−1.48 (2H, m), 2.31 (1H, br s), 2.48 (1H, ddd, *J* = 8.8, 6.4, 2.0 Hz), 3.48 (1H, br s), 3.98 (1H, m), 5.10 (1H, dd, *J* = 17.2, 1.8 Hz), 5.13 (1H, d, *J* = 6.2 Hz), 5.18 (1H, dd, *J* = 10.4, 1.8 Hz), 5.89 (1H, ddd, *J* = 17.2, 10.4, 9.2 Hz), 6.98 (2H, m), 7.24 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.6, 25.8, 29.2, 29.5, 29.5, 31.8, 34.9, 55.4, 71.6, 72.9, 119.2, 123.9, 124.5, 126.6, 134.1, 147.7; IR (film, cm^{-1}) 3337, 3073, 2924, 1027; HRMS (ESI+) calcd for $C_{17}H_{28}NaO_2S$ $(M + Na)^+$ 319.1702, found 319.1714.

(1*R*,2*R*,3*S*)-1-(Thiophen-2-yl)-2-vinylundecane-1,3-diyl Diacetate (10). Anhydrous Et_3N (2.25 mL, 16.5 mmol), Ac_2O (1.55 mL, 16.5 mmol), and 4-DMAP (catalytic amount) were added to a solution of **9** (0.642 g, 2.2 mmol) in anhydrous CH_2Cl_2 (10 mL) under N_2. The reaction was stirred for 2 h. HCl (2 N, 10 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with 1 N NaOH (10 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum to yield **10** as a colorless oil (0.799 g 2.1 mmol, 95%): R_f (hexanes/AcOEt 9:1) 0.88; $[\alpha]_D^{25}$ +9.7 (*c* 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (3H, t, *J* = 6.4 Hz), 1.23−1.35 (12H, m), 1.42−1.62 (2H, m), 2.03 (3H, s), 2.04 (3H, s), 2.75 (1H, td, *J* = 10.0, 2.4 Hz), 4.94 (1H, ddd, *J* = 17.2, 1.7 Hz), 5.11 (1H, dd, *J* = 10.2, 1.7 Hz), 5.29 (1H, ddd, *J* = 8.8, 2.4, 1.6 Hz), 5.60 (1H, dt, *J* = 17.2, 10.2 Hz), 5.97 (1H, d, *J* = 10.2 Hz), 6.90 (1H, m), 6.99 (1H, m), 7.23 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 21.0, 21.0, 22.6, 25.3, 29.2, 29.4, 29.5, 31.8, 32.7, 53.0, 69.5, 71.3, 121.1, 125.5, 126.3, 127.0, 131.9, 142.1, 170.0, 170.6; IR (film, cm^{-1}) 3076, 2925, 1740, 1237; HRMS (ESI+) calcd for $C_{21}H_{32}NaO_4S$ $(M + Na)^+$ 403.1914, found 403.1920.

(1*R*,2*R*,3*S*)-2-(2-Hydroxyethyl)-1-(thiophen-2-yl)undecane-1,3-diyl Diacetate (11). A solution of **10** (0.300 g, 0.78 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise to a stirred suspension of dicyclohexylborane (0.297 g, 1.7 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0 °C in a dry flask under N_2. After 10 min at 0 °C, the reaction was allowed to warm to rt and the mixture was stirred for 4 h. A solution of H_2O_2 (1.5 mL, 33%) and phosphate buffer (1.5 mL, pH = 7) was added, and the mixture was stirred for 2 h. The volatiles were removed under vacuum, and purification by column chromatography (silica gel, hexanes/AcOEt 85:15) afforded product **11** as a colorless oil (0.270 g, 0,68 mmol, 87%): R_f (hexanes/AcOEt 85:15) 0.5; $[\alpha]_D^{25}$ +22.1 (*c* 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (3H, t, *J* = 6.4 Hz), 1.23−1.35 (12H, m), 1.50−1.60 (3H, m), 1.69−1.77 (1H, m), 2.03 (3H, s), 2.04 (3H, s), 2.23 (1H, dtd, *J* = 10.0, 4.8, 2.4 Hz), 3.47 (2H, m), 5.26 (1H, ddd, *J* = 8.0, 5.6, 2.4 Hz), 5.94 (1H, d, *J* = 10.0 Hz), 6.95 (1H, m), 7.07 (1H, m), 7.27 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 21.1, 25.8, 29.1, 29.2, 29.4, 29.4, 31.8, 32.1, 43.4, 60.8, 70.8, 72.5, 125.7, 126.6, 127.0, 142.1, 167.0, 170.7; IR (film, cm^{-1}) 3467, 3075, 2923, 1736, 1235; HRMS (ESI+) calcd for $C_{21}H_{34}NaO_5S$ $(M + Na)^+$ 421.2019, found 421.205.

(2*R*,3*R*)-2-Acetoxy-3-[(*S*)-1-acetoxynonyl]pentanedioic Acid (12). Ruthenium(III) chloride monohydrate (5 mg, 0.0197 mmol) was added to a solution of **11** (0.147 g, 0.39 mmol) and $NaIO_4$ (0.760 g, 3.55 mmol) in CCl_4 (3 mL), CH_3CN (3 mL), and H_2O (4 mL), and

dx.doi.org/10.1021/jo302598h | *J. Org. Chem.* 2013, 78, 1519−1524

the mixture was stirred vigorously until TLC showed complete conversion. A saturated aqueous solution of Na_2CO_3 (5 mL) was added, and the layers were separated. The aqueous layer was acidified with 1N HClto pH = 2 and was extracted with AcOEt (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to yield **12** as a colorless oil (0.121 g, 0.323 mmol, 82%): R_f (CH_2Cl_2/MeOH 9:1) 0.1; ^{1}H NMR (CD_3OD, 400 MHz) δ 0.89 (3H, t, J = 7.2 Hz), 1.23−1.35 (12H, m), 1.55−1.69 (2H, m), 2.03 (3H, s), 2.11 (3H, s), 2.49 (2H, d, J = 6.4 Hz), 2.81 (1H, q, J = 6.4 Hz), 5.04 (1H, d, J = 5.2 Hz), 5.13 (1H, q, J = 5.2, Hz); ^{13}C NMR (CD_3OD, 100 MHz) δ 14.5, 20.6, 20.9, 23.8, 26.6, 30.4, 30.3, 30.6, 32.2, 33.1, 33.3, 40.9, 73.7, 74.1, 171.9, 172.2, 172.3, 175.6; IR (film, cm^{-1}) 3300−2500, 2921, 1737, 1702, 1248; HRMS (ESI+) calcd for $C_{18}H_{30}NaO_8$ $(M + Na)^+$ 397.1833, found 397.1841.

(3a*R*,4*S*,6a*R*)-4-Octyldihydrofuro[3,4-*b*]furan-2,6(3*H*,6a*H*)-dione (2). H_2SO_4 (1 N, 2 mL) was added to acid **12** (0.070 g, 0.19 mmol) in dioxane (4 mL), and the mixture was heated at reflux for 24 h. After cooling, the solvents were removed and CH_2Cl_2 (5 mL) and saturated aqueous Na_2CO_3 (5 mL) were added. After stirring for 30 min, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic combined organic extracts were dried over $MgSO_4$, and the solvents were removed. Chromatographic purification (silica gel, CH_2Cl_2/MeOH 99:1) gave **2** as a colorless solid (0.036 g, 0.14 mmol, 71%): R_f (CH_2Cl_2/MeOH 98:2) 0.9; $[\alpha]_D^{25}$ −8.6 (c 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (3H, t, J = 6.8 Hz), 1.24−1.37 (10H, m), 1.47−1.59 (3H, m), 1.78−1.86 (1H, m), 2.63 (2H, d, J = 9.6 Hz), 3.46 (1H, qd, J = 9.6, 5.8 Hz), 4.60 (1H, td, J = 8.4, 5.8 Hz), 5.14 (1H, d, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.6, 25.4, 26.8, 29.1, 29.2, 29.3, 31.4, 31.7, 39.4, 76.9, 78.7, 170.5, 173.6; IR (film, cm^{-1}) 2914, 2847, 1780, 1733; HRMS (ESI+) calcd for $C_{14}H_{26}NO_4$ $(M + NH_4)^+$ 272.1856, found 272.1851.

(−)-Isoavenaciolide ((−)-1). Magnesium methyl carbonate (2.0 M in DMF, 3.5 mL) was added to **2** (0.045 g, 0.18 mmol), and the mixture was heated at 140° for 6 h under N_2. After cooling, the mixture was carefully added to cold, stirred 6 N HCl (5 mL) and CH_2Cl_2. When vigorous gas evolution had subsided, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extracts were washed with H_2O (10 mL), dried over $MgSO_4$, and the solvents were removed. The residual yellow oil was treated with a solution of glacial acetic acid (1 mL), formalin (1 mL), *N*-methylaniline (0.5 mL), and sodium acetate (0.040 g). The mixture was stirred vigorously for 2 h at rt and then was diluted with a mixture of saturated NaCl and concentrated HCl (5:1) and CH_2Cl_2 (5 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic extracts were dried over $MgSO_4$, and the solvents were removed. Purification by column chromatography (silica gel, hexanes/AcOEt 7:3) afforded of (−)-isoavenaciolide ((−)-**1**) (0.038 g, 0.14 mmol, 78%) as a white solid: mp 126−128 °C; R_f (hexanes/AcOEt 8:2) 0.05; $[\alpha]_D^{25}$ −153.9 (c 0.99, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (3H, t, J = 6.4 Hz), 1.25−1.50 (10H, m), 1.52−1.71 (4H, m), 3.99 (1H, tt, J = 8.4, 2.2 Hz), 4.78 (1H, ddd, J = 9.6, 8.4, 3.2 Hz), 5.10 (1H, d, J = 8.4 Hz), 5.88 (1H, d, J = 2.2 Hz), 6.61 (1H, d, J = 2.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.6, 26.0, 29.1, 29.1, 29.3, 31.8, 32.4, 41.7, 74.7, 80.4, 128.9, 130.8, 167.8, 170.0; IR (film, cm^{-1}) 3021, 2932, 2843, 1793; HRMS (ESI+) calcd for $C_{15}H_{26}NO_4$ $(M + NH_4)^+$ 284.1856, found 284.1854.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of **1**, **2**, and **4**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel.: +34 934039114. Fax: +34 933397878. E-mail: xariza@ub.edu, jordigarciagomez@ub.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Spanish Ministerio de Educación y Ciencia (CTQ2006-13249 and CTQ2009-09692). We thank the Generalitat de Catalunya for a doctorate studentship to C.S., and the University of Barcelona for a fellowship to D.S. We also thank Anna Pou for assistance in the preparation of some starting materials. The authors are grateful to Novozymes Spain SA for a generous gift of Novozym 435.

■ REFERENCES

(1) Aldridge, D. C.; Turner, W. B. *J. Chem. Soc., C* **1971**, 2431−2432.
(2) Ueda, K.; Usui, T.; Nakayama, H.; Ueki, M.; Takio, K.; Ubukata, M.; Osada, H. *FEBS Lett.* **2002**, *525*, 48−52.
(3) For a review, see: Martín, V. S.; Rodríguez, C. M.; Martín, T. *Org. Prep. Proced. Int.* **1998**, *30*, 291−324.
(4) (a) Ohrui, H.; Emoto, S. *Tetrahedron Lett.* **1975**, *16*, 3657−3660. (b) Anderson, R. C.; Fraser-Reid, B. *Tetrahedron Lett.* **1977**, *18*, 2865−2868. (c) Anderson, R. C.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 4781−4786. (d) Wee, A. G. H. *Tetrahedron* **1990**, *46*, 5065−5076. Correction: Wee, A. G. H. *Tetrahedron* **1993**, *49*, 1335. For formal syntheses, see: (e) McDonald, C. E.; Dugger, R. W. *Tetrahedron Lett.* **1988**, *29*, 2413−2416. (f) Chida, N.; Tobe, T.; Suwama, M.; Ohtsuka, M.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1990**, 994−995. (g) Chida, N.; Tobe, T.; Suwama, M.; Ohtsuka, M.; Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2667−2673. (h) For the (+)-enantiomer, see: Alcázar, E.; Kassou, M.; Matheu, I.; Castillón, S. *Eur. J. Org. Chem.* **2000**, 2285−2289. (i) For other synthetic approaches, see: Al-Tel, T. H.; Al-Qawasmeh, R. A.; Sabri, S. S.; Voelter, W. *J. Org. Chem.* **2009**, *74*, 4690−4696 and references therein.
(5) (a) Suzuki, K.; Miyazawa, M.; Shimazaki, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1986**, *27*, 6237−6240. (b) Suzuki, K.; Miyazawa, M.; Shimazaki, M.; Tsuchihashi, G. *Tetrahedron* **1988**, *44*, 4061−4072. (c) Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D. *J. Org. Chem.* **1992**, *57*, 2228−2235. (d) Rodríguez, C. M.; Martín, V. S.; Martín, T. *J. Org. Chem.* **1996**, *61*, 8448−8452. For formal syntheses, see: (e) Ito, K.; Fukuda, T.; Katsuki, T. *Synlett* **1997**, 387−389. (f) Ito, K.; Fukuda, T.; Katsuki, T. *Heterocycles* **1997**, *46*, 401−411.
(6) (a) Yu, C.-M.; Youn, J.; Jung, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1553−1556. (b) For a formal synthesis, see: Labeeuw, O.; Blanc, D.; Phansavath, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Eur. J. Org. Chem.* **2004**, 2352−2358. (c) For a recent synthetic approach, see: Blot, V.; Reboul, V.; Metzner, P. *Eur. J. Org. Chem.* **2006**, 1934−1939.
(7) Sánchez, C.; Ariza, X.; Cornellà, J.; Farràs, J.; Garcia, J.; Ortiz, J. *Chem.—Eur. J.* **2010**, *16*, 11535−11538.
(8) For the use of allenes in natural product syntheses, see: Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074−3112.
(9) (a) Ma, S.; Hou, H.; Zhao, S.; Wang, G. *Synthesis* **2002**, 1643−1645. (b) Kuang, J.; Ma, S. *J. Org. Chem.* **2009**, *74*, 1763−1765.
(10) (a) Raminelli, C.; Comasseto, J. V.; Andrade, L. H; Porto, A. L. M. *Tetrahedron: Asymmetry* **2004**, *15*, 3117−3122. (b) Xu, D.; Li, Z.; Ma, S. *Tetrahedron Lett.* **2003**, *44*, 6343−6346.
(11) Enantiomeric excess was determined by HPLC analysis of the benzoyl derivatives of **5**.
(12) The *anti*,*anti* isomer is obtained when an aliphatic aldehyde is used under these conditions. This relative stereochemistry results from the addition of the (*Z*)-2-alkenylborane to the opposite face of the aldehyde.
(13) Relative stereochemistry was determined by analysis of ^{1}H NMR coupling constants (see Supporting Information of ref 7). The *syn* relationship between C*H*OTBS and C*H*CH=CH_2 is usually characterized by a J < 3 Hz (J = 2.0 Hz for compound **8** compared to J > 6 Hz for the *anti* relationship), whereas the *anti* relationship between C*H*CH=CH_2 and C*H*Ar is usually characterized by a $J \approx 9-10$ Hz (J = 9.0 Hz for compound **8** compared to $J \approx 4-8$ Hz for the *syn* relationship).

(14) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.
(15) Murta, M. M.; de Azevedo, M. B. M.; Greene, A. E. *Synth. Commun.* **1993**, *23*, 495−503.