Título artículo / Títol article:	Stereoselective synthesis of a C1−C18 fragment of amphidinolides G and H
Autores / Autors	García Fortanet, Jorge ; Formentín, Pilar ; Díaz Oltra, Santiago ; Murga Clausell, Juan ; Carda, Miguel ; Marco, J. Alberto
Revista:	Tetrahedron Volume 69, Issue 15, 15 April 2013
Versión / Versió:	Postprint de l'autor
Cita bibliográfica / Cita bibliogràfica (ISO 690):	GARCÍA-FORTANET, Jorge, et al. Stereoselective synthesis of a C1−C18 fragment of amphidinolides G and H . Tetrahedron , 2013, 69.15: 3192-3196
url Repositori UJI:	http://hdl.handle.net/10234/88089

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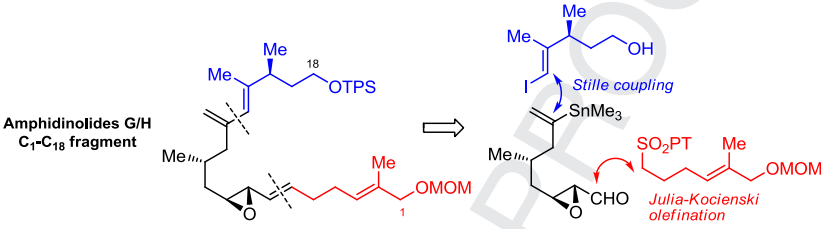
Graphical Abstract

Stereoselective synthesis of a C1–C18 fragment of amphidinolides G and H **pp 1–5**

Jorge García-Fortanet, Pilar Formentín, Santiago Díaz-Oltra, Juan Murga, Miguel Carda*, J. Alberto Marco*



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Please cite this article in press as: García-Fortanet, J.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.02.062

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Stereoselective synthesis of a C1–C18 fragment of amphidinolides G and H

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ARTICLE INFO

Article history:
Received 3 January 2013
Received in revised form 9 February 2013
Accepted 18 February 2013
Available online xxx

Keywords:
Macrolides
Amphidinolides
Julia–Kocienski olefination
Stille coupling
Ohira–Bestmann reaction
Alkyne silylstannation

ABSTRACT

A stereoselective synthesis of a C1–C18 segment of the structure of the cytotoxic macrolides amphidinolides G and H is reported. The target compound was retrosynthetically disconnected into three fragments. In the synthetic sense, connection of the fragments was made by means of a Stille coupling and a Julia–Kocienski olefination. Precursors from the chiral pool were used as the starting materials.

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1. Introduction

Marine microorganisms belonging to several phyla have attracted the attention of natural product chemists because of their role as the actual producers of many bioactive metabolites, initially found in, and deemed specific to, various marine microorganisms.[1] Amongst these metabolites, the amphidinolides are a family of macrolides isolated from marine dinoflagellates of the *Amphidinium* genus that are symbiotic to *Amphiscolops* flatworm species.[2] These macrolides have been found to display a range of pharmacological properties, most particularly cytotoxicity against several tumoral cell lines. Amphidinolides G **1** and H **2** (Fig. 1, now renamed G_1 and H_1) have been shown to be very potent in this aspect (IC_{50}<1 nm), a feature, which renders these compounds promising for cancer chemotherapy. In the specific case of amphidinolide H, its pharmacological action has been related to its ability to covalently bind on actin subdomain 4 with subsequent stabilization of the actin filaments.[3] In view of these pharmacological properties, it is not surprising that the amphidinolides have attracted considerable interest from the synthetic community. Indeed, many total syntheses of various amphidinolides have already been reported.[4]

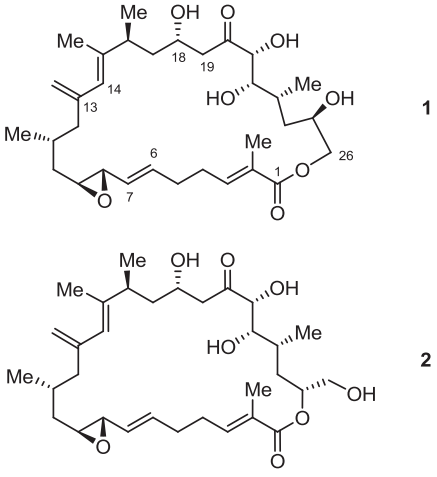

Fig. 1. Structures of amphidinolides G (**1**) and H (**2**).

For the reasons stated above, we have been interested in performing a stereoselective synthesis of macrolides **1** and **2**. Hydrolytic lactone ring-opening of these two isomeric lactones would give the same open-chain hydroxy acid. Herein, we report a short

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0040-4020/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tet.2013.02.062

synthesis of a C_1–C_{18} fragment common to these two natural compounds.[5,6]

Our retrosynthetic analysis for **1**, also valid for **2**, is shown in Fig. 2. Scission of the C_1–O and C_{18}–C_{19} bonds via lactone ring-opening and retroaldol cleavage gives rise to compounds **3** (fragment C_1–C_{18}), our present target, and **4** (fragment C_{19}–C_{26}), which has previously been prepared by us.[5e] Further bond scissions in **3** at C6=C7 via Julia–Kocienski olefination[7] and at C_{13}–C_{14} via Stille coupling[8] lead to the synthetic subtargets **5**–**8**.

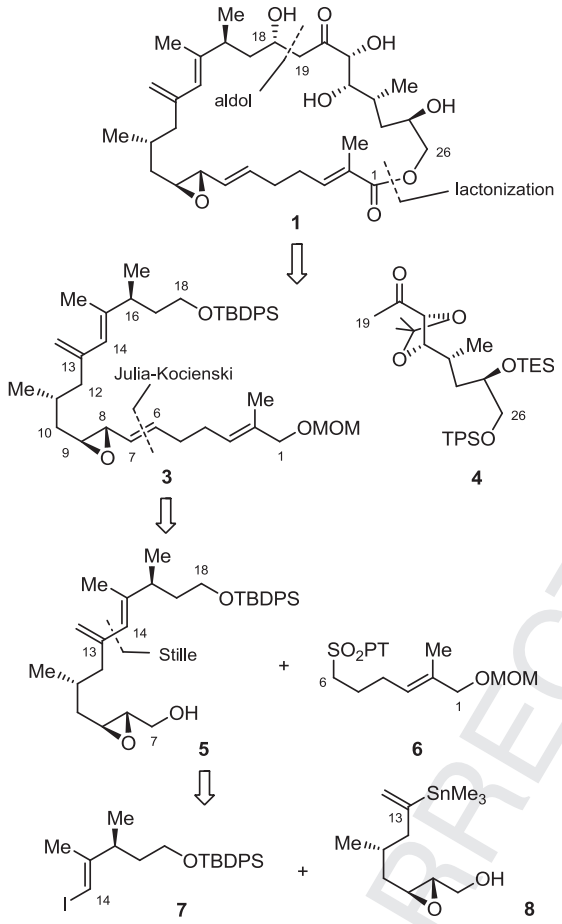


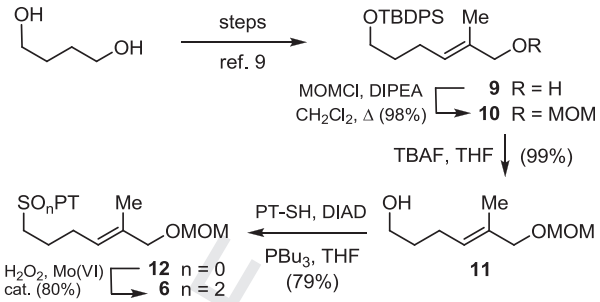
Fig. 2. Retrosynthetic disconnection of amphidinolide G (**1**) (for acronyms and abbreviations, see below).

2. Results and discussion

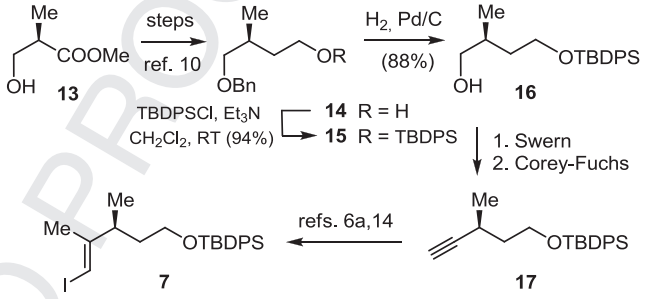
The synthesis of tetrazolyl sulfone **6** was performed as depicted in Scheme 1. Conversion of 1,4-butanediol into the known primary allylic alcohol **9** was performed in 4 steps following literature procedures.[9] Alcohol protection in **9** afforded **10**, which was desilylated to primary alcohol **11**. The latter was then converted into **6** by means of a standard procedure via sulfide **12**.

The known iodide **7** was prepared as shown in Scheme 2. The chiral and commercially available ester **13** was first converted into the known primary alcohol **14**.[5f] Silylation of **14** gave **15**, which was then hydrogenolytically debenzylated to **16**.[10] Swern oxidation[11] of the alcohol group in **16** followed by Corey–Fuchs homologation[12] of the intermediate aldehyde gave alkyne **17**,[13] which was then converted into vinyl iodide **7** through the previously reported carbometallation–iodination sequence.[6a,13]

For the preparation of alcohol **8**, we initially used alcohol **16** as the starting material (Scheme 3). Mesylation of **16** and treatment of the resulting mesylate with potassium cyanide in DMSO gave nitrile **18**, which was subsequently reduced to the corresponding

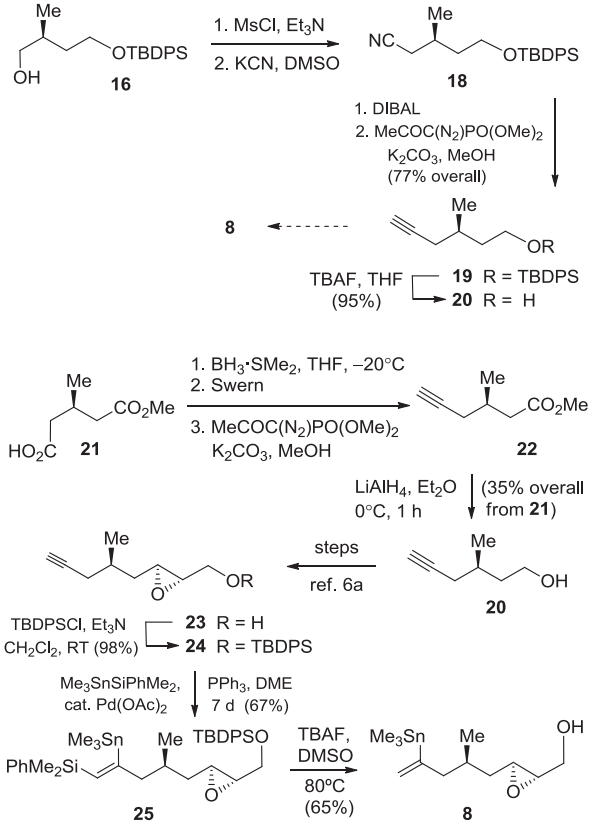


Scheme 1. Synthesis of sulfone **6**. Acronyms and abbreviations: TBDPS, *tert*-butyldiphenylsilyl; MOM, methoxymethyl; DIPEA, *N*,*N*-diisopropyl ethylamine; TBAF, tetrabutylammonium fluoride; PT, 1-phenyl-1*H*-tetrazol-5-yl; DIAD, diisopropyl azodicarboxylate.



Scheme 2. Synthesis of iodide **7**. Acronyms and abbreviations: Bn, benzyl.

aldehyde. Homologation of the latter to alkyne **19** was best performed in this case with the aid of the Ohira–Bestmann procedure.[14] Desilylation of **19** gave **20**, projected to be the next member in the sequence leading to **8**.



Scheme 3. Synthesis of epoxy alcohol **8**. Acronyms and abbreviations: Ms, methanesulfonyl; DME, 1,2-dimethoxyethane; DIBAL, diisobutyl-aluminum hydride; DMSO, dimethyl sulfoxide.

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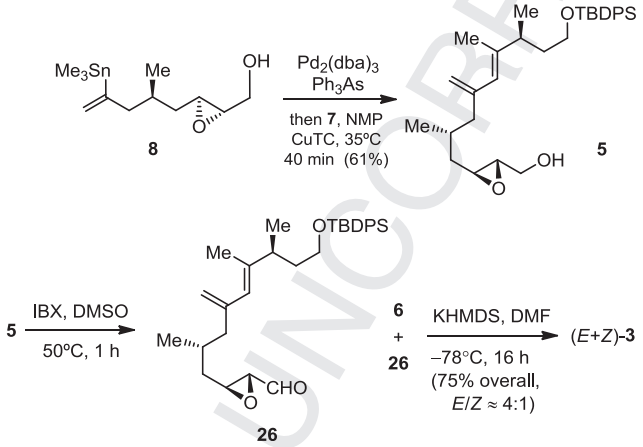
However, we found this reaction sequence too long (12 steps from the commercial ester **13**) and eventually replaced it by another more efficient one, also depicted in Scheme 3. The new sequence is based, with some modifications, on the one used by Cid and Pattenden[15] in their route toward amphidinolide B, with methyl hydrogen (*R*)-3-methylglutarate **21** as the chiral starting material. Borane reduction of the carboxy group to primary alcohol, Swern oxidation of the latter to the aldehyde[16] and Ohira–Bestmann homologation provided alkyne **22**.[17] Reduction of the ester to primary alcohol afforded alcohol **20** in only four steps from the commercially available precursor **21**.

Conversion of **20** into epoxy alcohol **23** was performed in four steps.[6a] Thus, the primary alcohol group of **20** was oxidized to the corresponding aldehyde, followed by Horner–Wadsworth–Emmons[18] olefination of the aldehyde, DIBAL reduction of the resulting conjugated ester to an allylic alcohol and Sharpless epoxidation[19] of the latter. Silylation of **23** gave **24**, which was then subjected to palladium-catalyzed silylstannation[20] to yield **25**. Treatment of the latter with TBAF caused both O- and C-desilylation and gave the desired **8**.

The next step was the Stille coupling[8] of **7** and **8**, which was performed as shown in Scheme 4. Epoxide **8** was dissolved in dry NMP and treated with $Pd_2(dba)_3$ and Ph_3As,[21] followed by addition of iodide **7** and CuTC.[22] This provided the desired diene **5** in 61% yield. Oxidation of the primary alcohol function in **5** to the corresponding aldehyde in **26** was best performed by means of IBX in DMSO.[23] Good conditions for the final coupling of **26** with sulfone **6** via Julia–Kocienski olefination were found only after extensive experimentation. The best results were found under the so-called Barbier conditions,[7] which led to the desired compound **3** in 75% yield as a ca. 4:1 *E*/*Z* mixture. Separation of these configurational isomers proved not feasible at this stage. We hope that further advance in the projected synthesis will permit the separation of the two isomers in a later intermediate.



Scheme 4. Synthesis of compound **3**. Acronyms and abbreviations: NMP, *N*-methylpyrrolidone; IBX, iodoxybenzoic acid; KHMDS, potassium hexamethyldisilylazide; DMF, *N*,*N*-dimethylformamide; CuTC, copper(I) thiophene-2-carboxylate.

In summary, compound **3**, which constitutes a C_1–C_{18} fragment of the structures of amphidinolides G/H, has been prepared in a stereoselective way. Coupling of this fragment with a C_{19}–C_{26} fragment previously reported by us[5e] will hopefully lead to the preparation of the complete structure of these two strongly cytotoxic lactones.

3. Experimental

3.1. General experimental features

See Supplementary data.

*3.1.1. (E)-6,13,13-Trimethyl-12,12-diphenyl-2,4,11-trioxa-12-silatetradec-6-ene (**10**).* A solution of alcohol **9**[9] (4.42 g, 12 mmol) in dry CH_2Cl_2 (60 mL) was treated at room temperature under N_2 with DIPEA (6.2 mL, 36 mmol) and MOMCl (1.82 mL, 24 mmol). The mixture was heated at reflux for 2 h. Work-up (extraction with CH_2Cl_2) followed by column chromatography on silica gel (hexanes/EtOAc, 8:2) afforded **10** (4.85 g, 98%) as a yellowish oil: ^{1}H NMR δ 7.80–7.75 (4H, br m), 7.50–7.40 (6H, br m), 5.52 (1H, br t, $J\sim$6.8 Hz), 4.68 (2H, s), 4.00 (2H, br s), 3.77 (2H, t, J=6.2 Hz), 3.44 (3H, s), 2.25 (2H, br q, $J\sim$7.5 Hz), 1.75 (3H, br s), 1.75–1.70 (2H, m), 1.16 (9H, s); ^{13}C NMR δ 134.0 (×2), 131.9, 19.2 (C), 135.5 (×4), 129.5 (×2), 128.1, 127.5 (×4) (CH), 95.2, 73.2, 63.3, 32.3, 24.0 (CH_2), 55.1, 26.8 (×3), 13.9 (CH_3); HR FABMS *m*/*z* 435.2344 (M+Na$^+$), calcd for $C_{25}H_{36}NaO_3Si$, 435.2331.

*3.1.2. (E)-6-(Methoxymethoxy)-5-methylhex-4-en-1-ol (**11**).* A solution of compound **10** (4.54 g, 11 mmol) in dry THF (70 mL) was treated under N_2 with TBAF (3.45 g, 13.2 mmol). The mixture was stirred at room temperature for 2 h. Removal of all volatiles under reduced pressure was followed by column chromatography of the residue on silica gel (hexanes/Et_2O, 1:1) to yield alcohol **11** (1.88 g, 99%) as a colorless oil: IR ν_{max} 3420 (br, OH) cm^{-1}; ^{1}H NMR δ 5.46 (1H, br t, $J\sim$7.3 Hz), 4.62 (2H, s), 3.93 (2H, br s), 3.65 (2H, t, J=6.4 Hz), 3.38 (3H, s), 2.14 (2H, br q, $J\sim$7.3 Hz), 1.67 (3H, br s), 1.65 (2H, br quint, $J\sim$7 Hz), 1.50 (1H, br s, OH); ^{13}C NMR δ 132.4 (C), 127.8 (CH), 95.4, 73.3, 62.5, 32.4, 24.0 (CH_2), 55.2, 14.0 (CH_3); HR FABMS *m*/*z* 197.1165 (M+Na$^+$), calcd for $C_9H_{18}NaO_3$, 197.1153.

*3.1.3. (E)-5-[(6-Methoxymethoxy-5-methylhex-4-en-1-yl)thio]-1-phenyl-1H-tetrazole (**12**).* A solution of alcohol **11** (1.74 g, 10 mmol) in dry THF (125 mL) was treated at 0 °C under N_2 with Bu_3P (5 mL, 20 mmol), 1-phenyl-1*H*-tetrazol-5-thiol (3.56 g, 20 mmol) and DIAD (4.92 mL, 25 mmol). The mixture was stirred at 0 °C for 1 h. Work-up (extraction with EtOAc) and column chromatography on silica gel (hexanes/EtOAc, 8:2) furnished sulfide **12** (2.64 g, 79%) as a yellowish oil: ^{1}H NMR δ 7.55–7.45 (5H, br m), 5.40 (1H, br t, $J\sim$7 Hz), 4.57 (2H, s), 3.89 (2H, br s), 3.35 (2H, t, J=7.2 Hz), 3.32 (3H, s), 2.18 (2H, br q, $J\sim$7.2 Hz), 1.88 (2H, br quint, $J\sim$7.2 Hz), 1.63 (3H, br s); ^{13}C NMR δ 154.2, 133.6, 133.2 (C), 130.0, 129.6 (×2), 126.1, 123.7 (×2) (CH), 95.3, 72.9, 32.7, 28.7, 26.4 (CH_2), 55.1, 14.0 (CH_3); HR FABMS *m*/*z* 357.1369 (M+Na$^+$), calcd for $C_{16}H_{22}N_4NaO_2S$, 357.1361.

*3.1.4. (E)-5-[(6-(Methoxymethoxy)-5-methylhex-4-en-1-yl)sulfonyl]-1-phenyl-1H-tetrazole (**6**).* A solution of sulfide **12** (1.67 g, 5 mmol) in EtOH (100 mL) was treated at 0 °C with $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (1.85 g, 1.5 mmol) and 30% H_2O_2 (5.6 mL, ~50 mmol). The mixture was stirred at room temperature for 16 h. The reaction was then quenched by addition of aqueous $Na_2S_2O_3$ (1.6 M, 100 mL). Work-up (extraction with EtOAc) and column chromatography on silica gel (hexanes/EtOAc, 8:2) afforded sulfone **6** (1.46 g, 80%) as a colorless oil: IR ν_{max} 1337, 1152 (SO_2) cm^{-1}; ^{1}H NMR δ 7.70–7.55 (5H, br m), 5.42 (1H, br t, $J\sim$7.3 Hz), 4.62 (2H, s), 3.93 (2H, br s), 3.72 (2H, br t, $J\sim$5.5 Hz), 3.37 (3H, s), 2.28 (2H, br q, $J\sim$7.3 Hz), 2.04 (2H, br quint, $J\sim$7.3 Hz), 1.67 (3H, br s); ^{13}C NMR δ 153.4, 134.7, 133.0 (C), 131.4, 129.7 (×2), 125.1, 124.6 (×2) (CH), 95.5, 72.8, 55.4, 25.9, 21.9 (CH_2), 55.3, 14.1 (CH_3); HR FABMS *m*/*z* 389.1269 (M+Na$^+$), calcd for $C_{16}H_{22}N_4NaO_4S$, 389.1259.

*3.1.5. (S)-[4-(Benzyloxy)-3-methylbutoxy](tert-butyl) diphenylsilane (**15**).* A solution of alcohol **14**[5f] (3.88 g, 20 mmol) in dry CH_2Cl_2

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(100 mL) was treated at 0 °C under N_2 with Et_3N (4.2 mL, 30 mmol), TPSCl (6.24 mL, 24 mmol) and DMAP (24 mg, 0.2 mmol). The mixture was then stirred at room temperature for 3 h. Work-up (extraction with CH_2Cl_2) and column chromatography on silica gel (hexanes/EtOAc, 95:5) gave silyl ether **15** (8.13 g, 94%) as a colorless oil: $[\alpha]_D$ −1.1 (*c* 1.35, $CHCl_3$); ^1H NMR δ 7.70–7.65 (4H, m), 7.40–7.25 (11H, br m), 4.45 (2H, s), 3.74 (2H, t, *J*=6.5 Hz), 3.33 (1H, dd, *J*=9, 5.8 Hz), 3.24 (1H, dd, *J*=9, 6.5 Hz), 2.00 (1H, apparent sextuplet, *J*~6.5 Hz), 1.76 (1H, apparent sextuplet, *J*~6.5 Hz), 1.40 (1H, apparent sextuplet, *J*~7 Hz), 1.08 (9H, s), 0.93 (3H, d, *J*=6.7 Hz); ^{13}C NMR δ 138.8, 134.1 (×2), 19.2 (C), 135.5 (×4), 129.5 (×2), 128.3 (×2), 127.6 (×4), 127.4 (×2), 127.3, 30.3 (CH), 75.8, 72.9, 62.1, 36.6 (CH_2), 26.9 (×3), 17.3 (CH_3); HR FABMS *m*/*z* 455.2365 ($M+Na^+$), calcd for $C_{28}H_{36}NaO_2Si$, 455.2382.

*3.1.6. (S)-4-(tert-Butyldiphenylsilyloxy)-2-methylbutan-1-ol (**16**).* Palladium hydroxide (20%, Degussa-type, 3 g) was suspended in EtOH (250 mL) under a H_2 atmosphere. After stirring at room temperature and ambient pressure for 15 min, a solution of compound **15** (6.49 g, 15 mmol) in EtOH (20 mL) was added via syringe. The mixture was then stirred for 90 min. When the starting compound was consumed (TLC monitoring), the reaction mixture was filtered through a Celite pad. The pad was then washed with EtOAc. The organic layers were evaporated to dryness and the residue was subjected to column chromatography on silica gel (hexanes/EtOAc, 3:1). This provided **16** (4.52 g, 88%) as a colorless oil having the reported physical and spectral properties.[10]

*3.1.7. (R)-tert-Butyl(3-methylhex-5-ynyloxy) diphenylsilane (**19**).* A solution of alcohol **16** (3.08 g, 9 mmol) in dry CH_2Cl_2 (40 mL) was treated at 0 °C under N_2 with Et_3N (2.5 mL, 18 mmol), MsCl (1.05 mL, 13.5 mmol), and DMAP (12 mg, 0.1 mmol). The mixture was then stirred at room temperature for 2 h. Work-up (extraction with CH_2Cl_2) gave a crude mesylate, which was dissolved in dry DMSO (45 mL) and treated under N_2 at room temperature with KCN (1.76 g, 27 mmol). The mixture was then stirred at 60 °C for 4 h. Work-up (extraction with Et_2O) afforded crude nitrile **18**, which was used as such in the next step: IR ν_{max} 2245 (C≡N) cm^{-1}; ^1H NMR δ 7.70–7.65 (4H, m), 7.45–7.35 (6H, m), 3.72 (2H, t, *J*=6 Hz), 2.38 (1H, dd, *J*=16.5, 5.4 Hz), 2.28 (1H, dd, *J*=16.5, 7 Hz), 2.15 (1H, m), 1.80–1.50 (2H, br m), 1.08 (3H, d, overlapped), 1.08 (9H, s).

A solution of **18** as obtained above in dry hexane (50 mL) was treated under N_2 at −78 °C with DIBAL (1 M solution in hexane, 12 mL, 12 mmol). The mixture was then stirred at −78 °C for 15 min. Work-up (extraction with Et_2O) gave an oily residue, which was dissolved in MeOH (15 mL) and treated at room temperature under N_2 with K_2CO_3 (2.2 g, 16 mmol) and freshly prepared Ohira–Bestmann's reagent (1.85 g, 9.6 mmol). The mixture was stirred overnight at room temperature. Work-up (extraction with Et_2O) and column chromatography on silica gel (hexanes-Et_2O, 8:2) furnished alkyne **19** (2.42 g, 77% overall for the four steps from **16**) as a yellowish oil: IR ν_{max} 3300 (C≡C) cm^{-1}; ^1H NMR δ 7.70–7.65 (4H, m), 7.45–7.35 (6H, m), 3.72 (2H, t, *J*=6.4 Hz), 2.19 (1H, ddd, *J*=16.5, 6, 2.5 Hz), 2.10 (1H, ddd, *J*=16.5, 6.5, 2.5 Hz), 2.00–1.85 (2H, m), 1.73 (1H, apparent sextuplet, *J*~6.5 Hz), 1.49 (1H, apparent sextuplet, *J*~6.5 Hz), 1.06 (9H, s), 1.00 (3H, d, *J*=6.6 Hz); ^{13}C NMR δ 133.3 (×2), 83.2, 19.4 (C), 135.6 (×4), 129.6 (×2), 127.6 (×4), 69.2, 29.1 (CH), 62.0, 38.5, 25.7 (CH_2), 26.9 (×3), 19.3 (CH_3).

*3.1.8. (R)-3-Methylhex-5-yn-1-ol (**20**).* A solution of alkyne **19** (2.1 g, 6 mmol) in dry THF (40 mL) was treated under N_2 with TBAF (1.72 g, 6.6 mmol). The mixture was stirred at room temperature for 2 h. Removal of all volatiles under reduced pressure was followed by column chromatography of the residue on silica gel (hexanes/Et_2O, 1:1) to yield **20** (639 mg, 95%) as a yellowish oil: $[\alpha]_D$ +4.2 (*c* 0.8, $CHCl_3$); IR ν_{max} 3400 (br, OH), 3300 (C≡C) cm^{-1}; ^1H NMR δ 3.67 (2H, m), 2.18 (1H, ddd, *J*=16.5, 6, 2.5 Hz), 2.13 (1H, ddd, *J*=16.5, 6.5, 2.5 Hz), 2.00 (1H, br s, OH), 1.96 (1H, t, *J*=2.5 Hz), 1.84 (1H, apparent sextuplet, *J*~6.5 Hz), 1.69 (1H, apparent sextuplet, *J*~6.5 Hz), 1.48 (1H, apparent sextuplet, *J*~6.5 Hz), 1.00 (3H, d, *J*=6.8 Hz); ^{13}C NMR δ 82.9 (C), 69.4, 29.1 (CH), 60.7, 38.6, 25.7 (CH_2), 19.4 (CH_3); HR EIMS *m*/*z* (rel int.) 97.0645 (M^+−Me, 11), 91 (26), 55 (100), calcd for $C_7H_{12}O$−Me, 97.0653.

3.1.9. tert-Butyl (2S,3S)-3-[(R)-2-methylpent-4-ynyl] oxiran-2-ylmethoxy diphenylsilane (24). A solution of alcohol **23**[6a] (617 mg, 4 mmol) in dry CH_2Cl_2 (40 mL) was treated at room temperature under N_2 with imidazole (408 mg, 6 mmol) and TPSCl (1.25 mL, 4.8 mmol). The mixture was then stirred at room temperature for 1 h. Work-up (extraction with CH_2Cl_2) and column chromatography on silica gel (hexanes/EtOAc, 95:5) gave silyl ether **24** (1.54 g, 98%) as a colorless oil: $[\alpha]_D$ −10.8 (*c* 0.65, $CHCl_3$); IR ν_{max} 3296 (C≡C) cm^{-1}; ^1H NMR δ 7.70–7.65 (4H, m), 7.45–7.35 (6H, m), 3.78 (2H, m), 2.91 (1H, td, *J*=4.5, 2 Hz), 2.84 (1H, td, *J*=6, 2 Hz), 2.24 (1H, ddd, *J*=16.5, 6, 2.5 Hz), 2.18 (1H, ddd, *J*=16.5, 6.5, 2.5 Hz), 1.99 (1H, t, *J*=2.5 Hz), 1.92 (1H, m), 1.69 (1H, dt, *J*=14, 6 Hz), 1.45 (1H, ddd, *J*=14, 8.3, 5.5 Hz), 1.08 (3H, d, overlapped), 1.07 (9H, s); ^{13}C NMR δ 133.3 (×2), 82.7, 19.2 (C), 135.6 (×2), 135.5 (×2), 129.8 (×2), 127.7 (×4), 64.2, 58.6, 54.9, 30.6 (CH), 69.6, 37.9, 26.1 (CH_2), 26.8 (×3), 19.3 (CH_3); HR FABMS *m*/*z* 393.2269 ($M+H^+$), calcd for $C_{25}H_{33}O_2Si$, 393.2249.

*3.1.10. Silylstannane **25**.* A solution of **24** (1.18 g, 3 mmol) in dry, degassed DME (25 mL) was treated at room temperature under N_2 with $PhMe_2Si$−$SnMe_3$ (900 mg, ~3 mmol),[20c] Ph_3P (140 mg, 0.54 mmol), and $Pd(OAc)_2$ (27 mg, 0.12 mmol). The mixture was then stirred at 35 °C for 7 d. After consumption of the starting material (TLC monitoring), the mixture was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel (hexanes/EtOAc, 98:2) to yield **25** (1.39 g, 67%) as a colorless oil: $[\alpha]_D$ −4.9 (*c* 0.8, $CHCl_3$); ^1H NMR δ 7.75–7.70 (4H, m), 7.56 (2H, m), 7.50–7.35 (9H, br m), 6.50 (1H, br s), 3.80 (2H, m), 2.90 (1H, td, *J*=4.5, 2 Hz), 2.85 (1H, td, *J*=6, 2 Hz), 2.50 (1H, dd, *J*=12.5, 6.3 Hz), 2.30 (1H, ddd, *J*=12.5, 7.5 Hz), 1.80–1.70 (2H, m), 1.36 (1H, ddd, *J*=14, 8.3, 5.5 Hz), 1.10 (9H, s), 0.98 (3H, d, *J*=6.5 Hz), 0.40 (6H, s), 0.09 (9H, s); ^{13}C NMR δ 167.2, 139.6, 133.3 (×2), 19.2 (C), 143.4 (×2), 135.6 (×4), 134.1 (×2), 129.8 (×2), 128.9, 127.7 (×5), 59.0, 55.0, 30.5 (CH), 64.3, 55.8, 38.5 (CH_2), 26.8 (×3), 19.4, −0.06 (×2), −6.8 (×3) (CH_3).

*3.1.11. (2S,3S)-3-[(S)-2-(Methyl-4-(trimethylstannyl) pent-4-enyl)oxiran-2-yl]methanol (**8**).* A solution of compound **25** (1.38 g, 2 mmol) in dry DMSO (50 mL) was treated under N_2 with TBAF (1 M solution in THF, 12 mL, 12 mmol). The mixture was stirred at 80 °C for 10 min and then at room temperature for 20 min. Work-up (extraction with Et_2O) and column chromatography on silica gel (hexanes/Et_2O, 1:1) furnished alcohol **8**[15] (415 mg, 65%) as a colorless oil: $[\alpha]_D$ −21.8 (*c* 0.8, $CHCl_3$); IR ν_{max} 3400 (br, OH) cm^{-1}; ^1H NMR δ 5.63 (1H, br s), 5.20 (1H, br d, *J*=2.5 Hz), 3.91 (1H, dd, *J*=12.5, 2.4 Hz), 3.63 (1H, dd, *J*=12.5, 4.3 Hz), 2.98 (1H, td, *J*=6, 2.2 Hz), 2.89 (1H, m), 2.34 (1H, dd, *J*=13.5, 6.6 Hz), 2.18 (1H, ddd, *J*=13.5, 7.7 Hz), 2.00 (1H, br s, OH), 1.75 (1H, m), 1.65 (1H, m), 1.30 (1H, m), 0.94 (3H, d, *J*=6.5 Hz), 0.14 (9H, s); ^{13}C NMR δ 154.3 (C), 58.9, 54.6, 30.7 (CH), 126.2, 61.6, 49.0, 38.4 (CH_2), 19.6, −9.5 (×3) (CH_3); HR EIMS *m*/*z* (rel int.) 305.0575 (M^+−Me, 22), 165 (100), calcd for $C_{12}H_{24}O_2Sn$−Me, 305.0558 (value calculated for ^{120}Sn, the most abundant isotope of tin).

*3.1.12. (2S,3S)-(3-[(2R,7S,E)-9-tert-Butyldiphenylsilyl-oxy-2,6,7-trimethyl-4-methylenenon-5-enyl]oxiran-2-yl)methanol (**5**).* A solution of epoxy alcohol **8** (383 mg, 1.2 mmol) in dry, degassed NMP (10 mL) was treated under N_2 at room temperature with Ph_3As (220 mg, 0.72 mmol) and $Pd_2(dba)_3$ (165 mg, 0.18 mmol). The

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reaction mixture was stirred under N_2 at room temperature for 15 min. Addition first of iodoalkene **7** (600 mg, 1.25 mmol) in dry, degassed NMP (15 mL) and then of CuTC (344 mg, 1.8 mmol) was followed by stirring under N_2 at 35 °C for 40 min. Work-up (extraction with Et_2O) and column chromatography on silica gel (hexanes/EtOAc, 8:2) furnished compound **5** (371 mg, 61%) as a yellowish oil: $[\alpha]_D$ −7.4 (*c* 1.24, $CHCl_3$); IR ν_{max} 3440 (br, OH) cm^{-1}; ^1H NMR δ 7.70–7.65 (4H, m), 7.45–7.35 (6H, m), 5.57 (1H, br s), 4.96 (1H, br s), 4.79 (1H, br s), 3.90 (1H, br d, $J\sim12$ Hz), 3.70–3.60 (3H, m), 2.91 (1H, td, J=6, 2 Hz), 2.86 (1H, m), 2.40 (1H, apparent sextuplet, $J\sim7$ Hz), 2.10 (1H, dd, J=12.5, 6.5 Hz), 1.94 (2H, br dd, $J\sim13.5$, 8 Hz, overlapping OH signal), 1.80–1.55 (5H, br m), 1.66 (3H, s), 1.07 (9H, s), 1.02 (3H, d, J=7 Hz), 0.90 (3H, d, J=6.8 Hz); ^{13}C NMR δ 144.3, 142.4, 134.1 (×2), 19.2 (C), 135.5 (×4), 129.5 (×2), 127.6 (×4), 125.2, 58.9, 54.7, 39.7, 29.6 (CH), 114.5, 62.4, 61.7, 45.8, 38.4, 37.7 (CH_2), 26.9 (×3), 19.7, 19.5, 14.1 (CH_3); HR EIMS *m*/*z* (rel int.) 506.3211 (M^+, 3), 449 (14), 431 (19), 199 (100), calcd for $C_{32}H_{46}O_3Si$, 506.3216.

3.1.13. Compound ***3****.* A solution of alcohol **5** (355 mg, 0.7 mmol) in dry DMSO (10 mL) was treated under N_2 at room temperature with IBX (392 mg, 1.4 mmol, 2 equiv). The reaction mixture was stirred under N_2 at 50 °C for 1 h. During the work-up, extraction with Et_2O had to be repeated 8–10 times, due to the slow extraction of the product with this solvent. Column chromatography on silica gel (hexanes/EtOAc, 7:3) provided aldehyde **26**, pure enough for use in the next step.

The material from the previous step and sulfone **6** (385 mg, 1.05 mmol) were dissolved under N_2 in dry DMF (15 mL). The solution was then cooled to −78 °C and treated dropwise with KHMDS (0.5 M in toluene, 2 mL, 1 mmol). The reaction mixture was then stirred overnight under N_2 at −78 °C. Work-up (extraction with Et_2O) and column chromatography on silica gel (hexanes/EtOAc, 8:2) afforded compound **3** (338 mg, 75% overall for the two steps) as a yellowish oil. NMR analysis revealed that the compound was an inseparable ∼80:20 mixture of *E*/*Z* stereoisomers. A small sample could be partially concentrated in the *E* isomer for analytical purposes: oil; ^1H NMR (signals of the major *E* stereoisomer) δ 7.70–7.65 (4H, m; TPS aromatic), 7.45–7.35 (6H, m; TPS aromatic), 5.90 (1H, dt, J=15.5, 6.5 Hz; H-6), 5.56 (1H, br s; H-14), 5.46 (1H, m; H-3), 5.20 (1H, dd, J=15.5, 8 Hz; H-7), 4.95 (1H, br s; C=CH_2), 4.76 (1H, br s; C=CH_2), 4.63 (2H, s; CH_2OMe), 3.94 (2H, br s; H-1/1′), 3.62 (2H, m; H-18/18′), 3.38 (3H, s; OMe), 3.00 (1H, dd, J=8, 2 Hz; H-8), 2.76 (1H, td, J=5.8, 2 Hz; H-9), 2.38 (1H, m; H-16), 2.20–2.05 (5H, br m; H-4/4′/5/5′/12), 1.92 (1H, br dd, J=13.5, 7.7 Hz; H-12′), 1.67 (3H, s; *Me*C_2 or *Me*C_{15}), 1.64 (3H, s; *Me*C_{15} or *Me*C_2), 1.80–1.50 (5H, br m; H-10/10′/11/17/17′), 1.06 (9H, s; ^{t}Bu), 1.01 (3H, d, J=6.8 Hz; *Me*C_{11} or *Me*C_{16}), 0.89 (3H, d, J=6.8 Hz; *Me*C_{16} or *Me*C_{11}); ^{13}C NMR (signals of the major *E* stereoisomer) δ 144.4, 142.3, 132.4 (×3), 19.2 (C), 135.5 (×4), 134.1, 129.5 (×2), 128.1, 127.6 (×4), 127.5, 125.3, 59.1 (×2), 39.7, 29.7 (CH), 114.4, 95.4, 73.2, 62.4, 45.9, 38.9, 37.7, 32.1, 27.2 (CH_2), 55.3, 29.6, 26.9 (×3), 19.7, 19.5, 14.1 (CH_3) (for atom numbering, see Fig. 2).

Acknowledgements

Financial support has been granted to M.C. by the Spanish Ministry of Education and Science (projects CTQ2008-02800 and CTQ2011-27560), by the Consellería dEmpresa, Universitat i Ciencia de la Generalitat Valenciana (projects ACOMP09/113) and by the BANCAJA-UJI Foundation (projects P1-1B-2008-14 and PI-1B2011-37).

Supplementary data

Supplementary data associated with this article (graphical NMR spectra) can be found in the online version. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.02.062.

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