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COMMUNICATION

Synthesis of the C45–C53 tetrahydropyran domain of norhalichondrins and the C14–C22 tetrahydrofuran domain of the halichondrin family†

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Sequential asymmetric α-aminoxylation of aldehydes and Horner–Wadsworth–Emmons olefination has been used as the key reaction for the synthesis of the C45–C53 tetrahydropyran domain of norhalichondrins and C14–C22 tetrahydrofuran domain of halichondrin family.

The halichondrins are a family of novel antimitotic polyether macrolides isolated from *Halichondria okadai* Kadota,[1,2] collected on the coast of Aburatsubo in the Miura Peninsula which is to the south of Tokyo. Since the isolation of norhalichondrin A (Fig. 1) in 1985, there has been substantial interest from chemists and biologists in the halichondrin family of compounds. Halichondrins have attracted significant scientific attention[3] because of their complex molecular architectures and their remarkable *in vitro* and *in vivo* antitumor activities.[4] Recently we have disclosed the synthesis of the C38–C54 spiroketal segment of halichondrin B from our group.[5] In continuation of our interest in the halichondrin family of compounds and our recent interest in the use of asymmetric α-aminoxylation reaction,[6] we herein report the synthesis of the C45–C53 fully functionalized tetrahydropyran- and tetrahydrofuran containing domains of the halichondrin family utilizing the sequential asymmetric α-aminoxylation of aldehydes and Horner–Wadsworth–Emmons (HWE) olefination reaction as the key step. Phillips *et al.*[3a,c] used functionalized furfural as the starting material for the preparation of the THP domain and ketoester *via* diazoketone intermediate for the THF domain respectively, whereas Kishi *et al.* [3b] used 2-deoxy-L-arabinose diethyl thioacetal 4,5-acetonide as the starting material for the preparation of the THF domain in 13 steps.

Retrosynthetic analysis for the C45–C53 tetrahydropyran containing domain **1** is depicted in Scheme 1. We envisaged that this tetrahydropyran domain **1** could be obtained *via* hydrolysis of the acetonide group in compound **2** followed by oxa-Michael cyclization reaction. Precursor **2** could be obtained from aldehyde **3** using asymmetric aminoxylation and HWE reaction. The aldehyde **3** in turn could be made from epoxy alcohol **4** *via* Gillman reaction and other functional group transformations. Epoxy alcohol **4** itself could be accessed from the known secondary allylic alcohol **5**[7] by chain elongation with Wittig ylide, DIBAL-H reduction followed by Sharpless epoxidation.

Our synthesis of the C45–C53 tetrahydropyran domain **1** of the norhalichondrins commenced with the known secondary allylic alcohol **5**[7] (Scheme 2). Accordingly, the secondary hydroxyl group in **5** was protected as methoxymethyl (MOM) ether to afford 6 in 85% yield. Next, compound **6** was subjected to one pot dihydroxylation, oxidative cleavage of diol (OsO_4/$NaIO_4$/THF/H_2O) to furnish the corresponding aldehyde, which on chain elongation using two carbon Wittig ylides gave α,β-unsaturated ester **7**. DIBAL-H

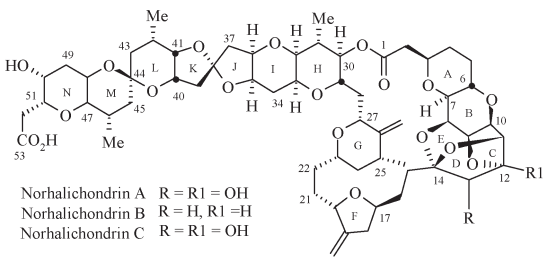
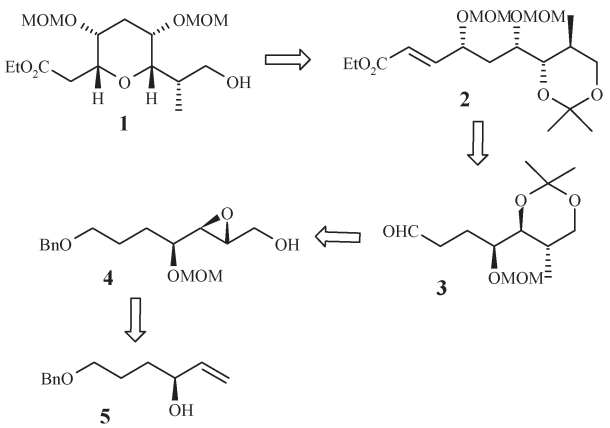


Fig. 1



Scheme 1 Retrosynthetic analysis.

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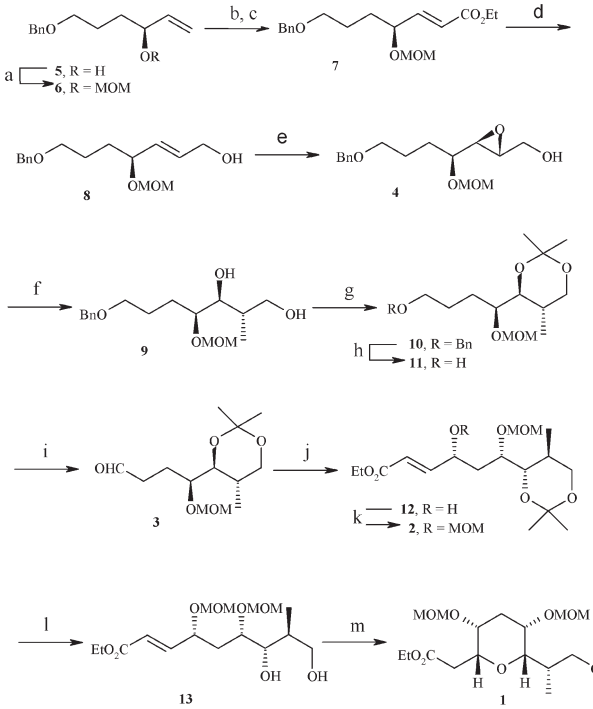
† Electronic supplementary information (ESI) available: spectral data of all new compounds. NOE and HPLC diagrams for selected compounds. See DOI: 10.1039/c2ra21346j



Scheme 2 reagents: a) MOMCl, N,N-diisopropylethyl amine, anhydrous CH_2Cl_2, 0 °C–r.t, 5 h, 85%; b) i) OsO_4, NMO, Acetone:H_2O (1 : 1), 48 h, 90%; c) i) $NaIO_4$, THF : H_2O (4 : 1), 30 min; ii) PPh_3 = $CHCO_2Et$, benzene, r.t., 3 h, (80% from 2 steps); d) DIBAL-H, anhydrous CH_2Cl_2, 0 °C–r.t., 1 h, 82%; e) (−)-DIPT, Ti(*i*OPr)$_4$, TBHP, anhydrous CH_2Cl_2, −20 °C, 36 h, 80%; f) i) Me_2CuLi, anhydrous Et_2O, −40 °C, 3.5 h; ii) $NaIO_4$, THF : H_2O (4 : 1), 0 °C–r.t., 30 min, 78%. g) 2,2-DMP, PPTS, anhydrous CH_2Cl_2, 0 °C–r.t., 3 h, 85%; h) Li, liq NH_3, anhydrous THF, −78 °C, 30 min, 82%; i) IBX, anhydrous CH_2Cl_2, anhydrous DMSO, 0 °C–r.t., 12 h, 80%; j) i) PhNO, L-Proline (40 mol %), triethyl phosphono acetate, Cs_2CO_3, anhydrous DMSO, r.t., 1 h, ii) Cu(OAc)$_2$, EtOH, r.t., 12 h, 57%, 91%de; k) MOMCl, N,N-diisopropylethyl amine, DMAP, anhydrous CH_2Cl_2, 0 °C–r.t., 7 h, 80%; l) PPTS, MeOH, r.t., 5 h, 85%; m) TBAF, anhydrous THF, r.t, 3 days, 75%.

reduction of the ester carbonyl group sets up the allyl alcohol **8** in 82% yield. Sharpless asymmetric epoxidation employing *D*-(–)-diisopropyl tartrate and TBHP furnished the desired epoxy alcohol **4** in 80% yield Regioselective opening of epoxide with lithium dimethylcuprate gave 1,3-diol compound **9** in 78% yield after removing the minor 1,2-diol compound by treatment with $NaIO_4$. Diol **9** was masked as an acetonide **10** using 2,2-dimethoxy propane and catalytic PPTS and then debenzylation with Li in liq NH_3 in dry THF provided primary alcohol **11**, which was oxidized to the corresponding aldehyde **3** using IBX in DMSO/CH_2Cl_2. The sequential α-aminoxylation-olefination on aldehyde **3** catalyzed by 40 mol% L-proline using nitroso benzene in DMSO at rt followed by *in situ* Horner–Wadsworth–Emmons olefination with triethylphosphono acetate and Cs_2CO_3 as base resulted in the formation of aminoxyolefinic ester, followed by cleavage of the O–N bond using Cu(OAc)$_2$ in ethanol at room temperature gave the γ-hydroxy α,β-unsaturated ester **12** with 91% de. The absolute stereochemistry of the new chiral center formed in compound **12** was confirmed at the later stage by NOE studies of compound **1** (see Fig. 2). The secondary hydroxy group was protected as a MOM ether to afford **2** in 80% yield. Hydrolysis of acetonide group under PPTS/MeOH conditions led to the free diol **13**, which on exposure to TBAF in dry THF produced the desired product, the C45–C53 tetrahydropyran domain **1** of norhalichondrins with the required *syn* relationship *via* intramolecular oxa-Michael reaction.

The structure of compound **1** was analyzed in pure $CDCl_3$ using 2D NMR techniques such as gDQCOSY, HSQC and NOESY. The experiential $^3J_{HH}$ couplings H_5–H_6 = 4.0 Hz (H_5 equatorial and H_6 axial) and H_2–H_3 = 1.9 Hz (H_2 axial and H_3 equatorial) are allowing to fix the axial and equatorial positions of the protons. Furthermore, observed NOE cross peaks between H_F–H_H, H_F–H_5, H_3–H_D, H_A–H_D, H_C–H_D and H_2–H_6 suggest the following structure for compound **1** (Fig. 2 and 3).

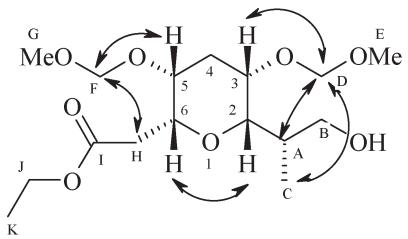


Fig. 2 Chemical structure of **1**.

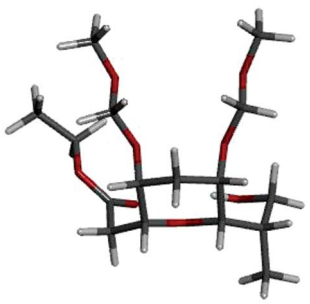
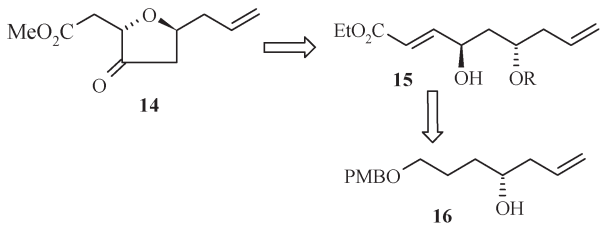


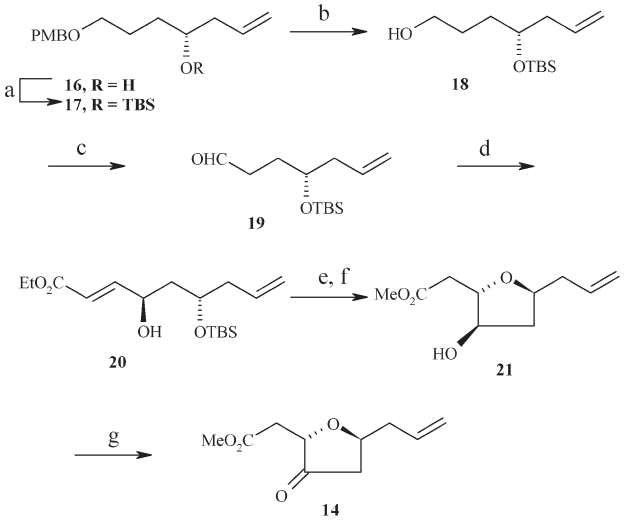
Fig. 3 Energy-minimized diagram for **1**.

Retrosynthetic analysis for the C14–C22 tetrahydrofuran domain **14** of the halichondrin family is presented in Scheme 3.

The synthesis of the C14–C22 tetrahydrofuran domain **14** of the halichondrin family starts from the known homoallyl alcohol **16**[8] (Scheme 4), which was eventually protected as TBS ether **17**. After deprotection of the PMB group, the resulting alcohol **18** was oxidized to an aldehyde **19**. The desired hydroxy unsaturated ester **20** was obtained using an aminoxylation reaction. Thus, treatment of aldehyde **19** with nitrosobenzene in the presence of 40 mol% of L-proline in DMSO at room temperature followed by *in situ* Horner–Wadsworth–Emmons olefination with triethylphosphono acetate and Cs_2CO_3 as base furnished an aminoxyolefinic ester; cleavage of the O–N bond using Cu(OAc)$_2$ in ethanol gave the γ-hydroxy α,β-unsaturated ester **20** in 52% yield with 98% de. The absolute stereochemistry of the new chiral center formed in compound **20** was confirmed at a later stage by NOE studies of compound **21** (see Fig. 4). TBS deprotection with TBAF followed by cyclization using Triton B in MeOH[9] for 48 h furnished the required *anti* 2,5-tetrahydrofuran **21** in 78% yield, where transesterification has taken place. The oxidation of the hydroxy group using IBX provided the desired C14–C22 tetrahydrofuran domain **14** of the halichondrin family in 70% yield.



Scheme 3 Retrosynthetic analysis.



Scheme 4 Reagents: a) TBSCI, imidazole, anhydrous CH_2Cl_2, 0 °C, 2 h, 92% b) DDQ, CH_2Cl_2 : H_2O (9 : 1), 0 °C, 30 min., 78%; c) IBX, anhydrous CH_2Cl_2, anhydrous DMSO, 0 °C–r.t., 10 h, 82%; d) i) PhNO, L-Proline (40 mol %), triethyl phosphonoacetate, Cs_2CO_3, anhydrous DMSO, r.t., 1 h; ii) $Cu(OAc)_2$, EtOH, r.t., 12 h, 52%, 98% de; e) TBAF, anhydrous THF, 0 °C–r.t, 30 min, 80%; f) Triton-B, MeOH, r.t., 1 h, 78%; g) IBX, anhydrous CH_2Cl_2, anhydrous DMSO, 0 °C–r.t., 2 days, 70%.

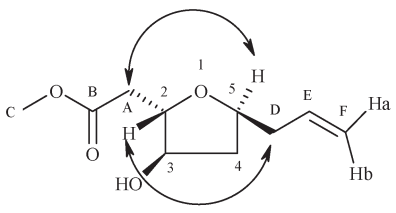


Fig. 4 Chemical structure of **21**.

The structure of compound **21** was analyzed in pure $CDCl_3$, by using 1D- ^1H and 2D ^1H NMR techniques such as gDQCOSY, HSQC and NOESY. Observed NOE cross peaks between H_5–H_A, H_2–H_D indicating H_2 and H_5 are *anti* to each other suggest the indicataed structure for compound **21** (Fig. 4 & 5).

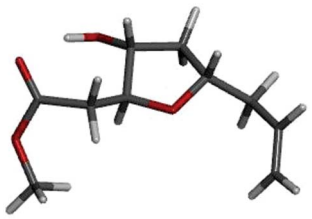


Fig. 5 Energy-minimized diagram for **21**.

In conclusion, synthesis of the C45–C53 tetrahydropyran domain of norhalichondrins and the C14–C22 tetrahydrofuran domain of the halichondrin family has been achieved in 13 linear steps with a overall 5.07% yield and in 7 linear steps with a overall 13.3% yield featuring MacMillan aminoxylation and HWE followed by oxa-Michael as the key reaction steps. Our group is engaged toward the synthesis of halichondrin and norhalichondrin and the results will be published in due course.

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