Synthesis of the macrocyclic core of iriomoteolide-1a†

Shuo Li,[a] Zheng Chen,[a] Zhengshuang Xu*[ab] and Tao Ye*[ab]

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The fully functionalized macrocyclic core of the marine natural product iriomoteolide-1a has been successfully constructed in a convergent and enantioselective manner.

Iriomoteolide-1a (Fig. 1) is a new member of a family of structurally related cytotoxic natural products isolated from strains of microscopic marine dinoflagellates.[1] Its structure is defined by a 20-membered macrolactone punctuated by nine stereogenic centers, three endogenous double bonds, one *exo*-methylene unit and one six-membered hemiketal ring.[2] Relative and absolute stereochemistry assignments were based on extensive NMR studies, including modified Mosher ester analysis. Iriomoteolide-1a displayed potent cytotoxicity against human B lymphocyte DG-75 cells (IC_{50}: 0.002 μg mL^{-1}) and Epstein–Barr virus (EBV)-infected human B lymphocyte Raji cells (IC_{50}: 0.003 μg mL^{-1}).[2] Owing to its interesting structural features and biological properties, iriomoteolide-1a has attracted the attention of synthetic chemists over the past three years. To date no total synthesis of iriomoteolide-1a has yet been reported. However, the preparation of fragments corresponding to C1–C9,[3a] C1–C12,[3b,c] C13–C23[3a,d–f] and C7–C23[3g,h] of iriomoteolide-1a has been disclosed. As part of a program directed toward the synthesis, structural modification, and biological evaluation of marine natural products,[4] we have developed and report herein a convergent, highly stereocontrolled approach to the macrocyclic core of iriomoteolide-1a.

As outlined in our retrosynthetic analysis, iriomoteolide-1a could be simplified by utilizing macrolactone **1** as the advanced precursor with the six-membered hemiketal ring being installed at a later stage in the total synthesis. It was envisaged that the 20-membered macrolactone **1** could be constructed by ruthenium-catalyzed ring closing metathesis (RCM) of the corresponding precursor which was planned to be assembled from three fragments of comparable complexity (Fig. 1). This strategy would confine protecting group operations and oxidation state adjustments to a minimum.

[a] *Laboratory of Chemical Genomics, Peking University Shenzhen Graduate School, University Town of Shenzhen, Xili, Nanshan District, Shenzhen, China 518055. E-mail: yet@szpku.edu.cn, xuzs@szpku.edu.cn*
[b] *Department of Applied Biology & Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, China. E-mail: bctaoye@inet.polyu.edu.hk; Tel: +852 34008722*

† Electronic supplementary information (ESI) available: Full details for experimental procedures for compounds **1–5**, **5a**, **6**, **6a**, **6b**, **7**, **7a**, **7b**, **8–9**, **9a**, **9b**, **10**, **10a**, **12a**, **13**, **13a**, **14–15**, **15a**, **15b**, **17–19**, **19a**, **20**, **20a**, **21**, **21a**, **21b** and **22** and ^1H and ^{13}C NMR spectra for compounds **1–5**, **5a**, **6–7**, **7a**, **8-9**, **9a**, **9b**, **10**, **10a**, **12a**, **13**, **14–15**, **15a**, **19**, **19a**, **20**, **20a**, **21**, **21a**, and **22**. See DOI: 10.1039/c0cc00915f

The synthesis of the sulfone-based fragment **2** commenced from α,β-unsaturated ester **5**, which is readily available in three steps starting from 1,3-propanediol.[5] Sharpless asymmetric dihydroxylation[6] of **5** followed by exposure of the resulting diol to dimethoxypropane and *p*-TsOH provided acetonide **6** in 97% yield (Scheme 1). DIBAL-H reduction of the methyl ester in **6** afforded the corresponding primary alcohol, which allowed for conversion to the terminal alkene (**7**) in 81% overall yield *via* Dess–Martin[7] oxidation and subsequent olefination with methylenetriphenylphsophorane.[8] The *p*-methoxybenzyl group was removed from **7** with DDQ, and the primary alcohol was converted into the corresponding aldehyde by Dess–Martin oxidation.[7] This material was then homologated to methyl ketone **8** using a two-step procedure including nucleophilic addition using MeMgBr and Dess–Martin oxidation. Boron-mediated 1,5-*anti* aldol reaction[9] was employed for the construction of β-hydroxy ketone **9**. Thus, the methyl ketone **8** was enolized using $(c\text{-Hex})_2BCl$ and Hünig's base at −78 °C. Addition of aldehyde **11** at −78 °C then gave the desired 1,5-*anti* adduct **9** in 85% yield and with no visible trace of the *syn* stereoisomer (dr > 50 : 1). Conversion of **9** to diene **10** was achieved by a three-step sequence of straightforward transformations: (i) oxidation of the PMB ether to the corresponding PMP acetal,[10] (ii) olefination with methylenetriphenylphosphorane,[8] and (iii) reductive opening of the PMP acetal with Dibal-H.[11] Mitsunobu reaction[12] of alcohol **10** with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) followed by oxidation with hydrogen peroxide and ammonium heptamolybdate tetrahydrate[13] furnished sulfone **2** in 97% yield (two steps).

The synthesis of fragment **3** started with the protection of the known chiral ester **12**[14] as its TBDPS ether, followed by DIBAL-H reduction of the methyl ester to afford alcohol **13** in 94% yield (Scheme 2). Oxidation with the Dess–Martin periodinane[7] and a subsequent Corey–Fuchs reaction[15]

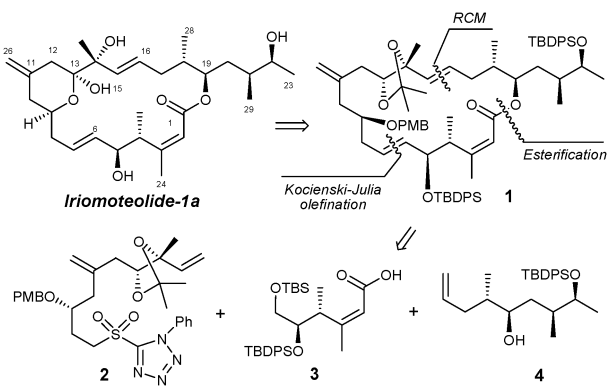
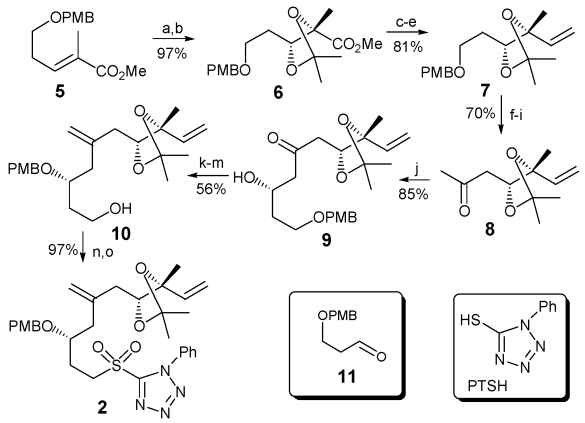


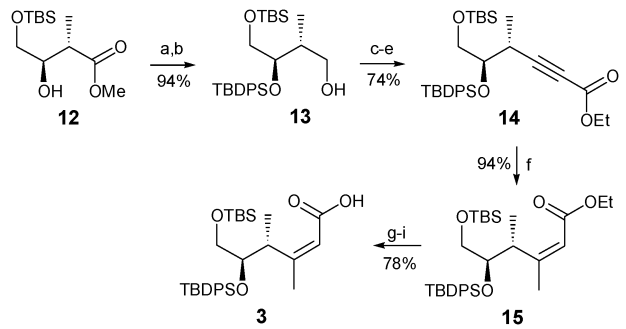
Fig. 1 Structure and retro-synthetic analysis of iriomoteolide-1a.



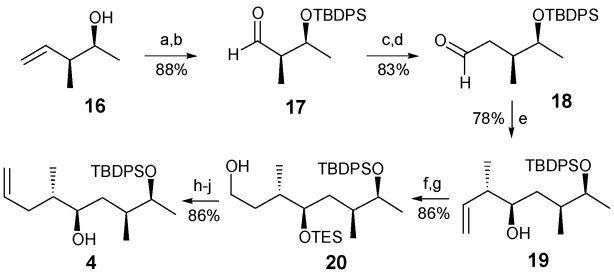
Scheme 1 (a) $K_3Fe(CN)_6$, AD-mix-β, $MeSO_2NH_2$; (b) 2,2-dimethoxypropane, TsOH; (c) DIBAL-H, THF; (d) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; (e) $CH_2{=}PPh_3$, THF; (f) DDQ, CH_2Cl_2–H_2O; (g) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; (h) CH_3MgI, Et_2O; (i) Dess–Martin periodinane, CH_2Cl_2; (j) *c*-Hex_2BCl, DIPEA then **11**, dr > 50 : 1; (k) DDQ, CH_2Cl_2; (l) $CH_2{=}PPh_3$, THF; (m) DIBAL-H, CH_2Cl_2; (n) PTSH, DIAD, PPh_3; (o) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, NaOAc, 50% H_2O_2/EtOH.

in which the anion was trapped with ethyl chloroformate established the acetylenic compound **14** in 74% yield over three steps. 1,4-Addition of Gilman's reagent to ester **14** furnished the alkene ester **15** in 94% yield.[16] To our surprise, attempts to hydrolyze ester **15** were unsuccessful. This ester was then converted into the corresponding acid **3** by the use of a three-step process involving DIBAL-H reduction of the ester to an allylic alcohol that was then subjected to sequential manganese dioxide and Pinnick[17] oxidations to afford the corresponding carboxylic acid **3**.

The preparation of the C16–C23 fragment **4** began with the protection of the known homoallylic alcohol **16**[18] as its TBDPS ether, followed by oxidative cleavage of the terminal alkene[19] to afford the corresponding aldehyde **17** in 88% yield over two steps (Scheme 3). Aldehyde **17** was then subjected to a Wittig olefination/acidic hydrolysis sequence,[20] which led to homologated aldehyde **18** in 83% yield. Aldehyde **18** was then reacted with Brown's (*E*)-crotyldiisopinocampheylborane prepared from (−)-diisopinocampheyl(methoxy)borane, and yielded the *anti*-homoallylic alcohol **19** in 78% yield,[18] with a



Scheme 2 (a) TBDPSCl, imidazole, DMAP, DMF; (b) DIBAL-H, THF, −78 to 0 °C; (c) Dess–Martin periodinane; (d) CBr_4, PPh_3, CH_2Cl_2; (e) *n*-BuLi, $ClCO_2Et$, THF; (f) MeLi, CuI, THF; (g) DIBAL-H, THF, −78 to 0 °C; (h) MnO_2, CH_2Cl_2; (i) $NaClO_2$, NaH_2PO_4, *t*-BuOH–H_2O.



Scheme 3 (a) TBDPSCl, imidazole, DMAP, DMF; (b) OsO_4, $NaIO_4$, 2,6-lutidine; (c) $MeOCH{=}PPh_3$, THF; (d) 5 N HCl, CH_2Cl_2–THF; (e) KOBu^t, *trans*-2-butene, *n*-BuLi, (−)-IPC_2BOMe, then $BF_3{\cdot}OEt_2$, **18**, −78 °C; 3 N NaOH, 30% H_2O_2; dr > 97 : 3; (f) TESOTf, 2,6-lutidine, CH_2Cl_2; (g) 9-BBN, 3 N NaOH, 30% H_2O_2; (h) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; (i) $CH_2{=}PPh_3$, THF; (j) 3 N HCl, CH_2Cl_2–THF.

diastereomeric ratio higher than 97 : 3. Protection of the secondary alcohol in **19** as its triethylsilyl ether, followed by alkene hydroboration/oxidation[21] with 9-borabicyclo[3.3.1]-nonane (9-BBN) and alkaline hydrogen peroxide furnished the corresponding alcohol **20** in 86% yield (over two steps). Dess–Martin oxidation of the primary alcohol in **20** to the corresponding aldehyde which was subjected to a Wittig olefination followed by removal of the TES-ether then completed the fragment **4** in 86% yield (over three steps).

With the three target fragments in hand, the stage was now set for their assembly and elaboration into macrocycle **1** (Scheme 4). Our fragment assembly began with coupling of fragments **3** and **4**. Thus, the esterification of alcohol **4** with carboxylic acid **3** was carried out under Yamaguchi conditions[22] to yield the corresponding ester which was then treated with pyridinium *p*-toluenesulfonate (PPTS) in EtOH–H_2O to afford alcohol **21** in 80% yield (over two steps). For the completion of the construction of RCM precursor **22**, alcohol **21** and sulfone **2** were connected by using an *E*-selective one-step Kocienski–Julia olefination.[23] Thus, Dess–Martin oxidation of **21** provided the corresponding crude aldehyde, which was treated with the anion derived from sulfone **2** and LiHMDS in DMF/HMPA at −50 °C, to provide alkene **22** with excellent *E*-selectivity ($E : Z$ > 10 : 1) in 75% yield. With tetraene **22** in hand, we proceeded to study the key RCM step for the formation of the 20-membered ring. Gratifyingly, exposure of **22** to Hoveyda–Grubbs' second-generation catalyst[24] in refluxing toluene delivered the desired macrocycle **1** as the only isolable product in 51% yield.

In summary, the carbocyclic skeleton of the marine natural product iriomoteolide-1a has been prepared *via* a convergent route that employed boron-mediated 1,5-*anti* aldol reaction, Yamaguchi esterification, Kocienski–Julia olefination and ring-closing metathesis as the key steps. The elaboration of macrolactone **1** to natural iriomoteolide-1a is ongoing in our laboratories and will be reported in due course. After acceptance of this manuscript for publication, Horne and coworkers reported a total synthesis of proposed structure of iriomoteolide-1a.[25]

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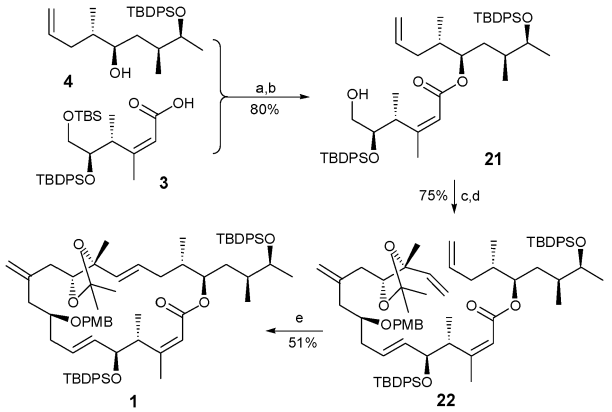

Scheme 4 (a) **3**, 2,4,6-trichlorobenzoyl chloride, Et_3N, then **4**, DMAP; (b) PPTS, EtOH–THF; (c) Dess–Martin periodinane, $NaHCO_3$; (d) **2**, LiHMDS, DMF–HMPA, then **21**; (e) Hoveyda–Grubbs' catalyst, toluene, reflux.

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