Synthetic Studies towards Iriomoteolide 1a: Stereocontrolled Construction of C1–C9 and C11–C23 Segments Using Lactate Aldol Chemistry

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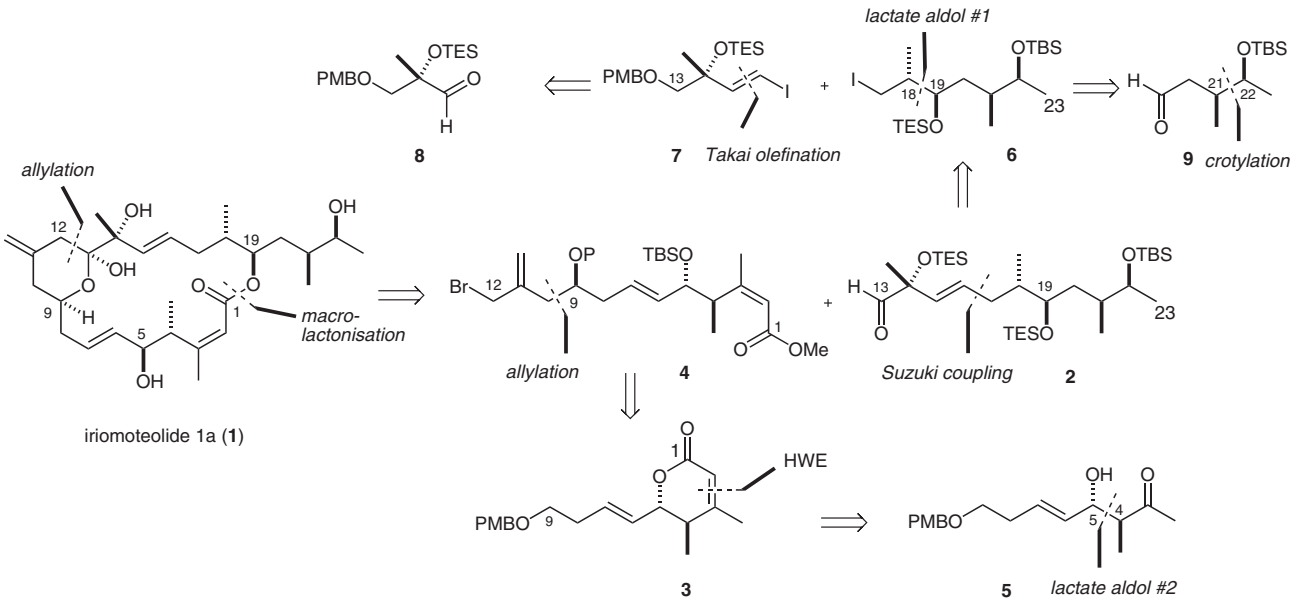
Dedicated to Professor Gerry Pattenden on the occasion of his 70th birthday

Abstract: The stereocontrolled construction of C1–C9 and C13–C23 segments of the cytotoxic macrolide iriomoteolide 1a is reported, exploiting boron aldol additions of enantiomeric lactate-derived ketones and a Suzuki–Miyaura cross-coupling reaction.

Key words: macrolide, anticancer, aldol reactions, cross-coupling, asymmetric synthesis

Marine macrolides with potent antimitotic properties represent promising lead structures for the development of new anticancer agents, provided a sustainable supply can be realised.[1] Dinoflagellates of the genus *Amphidinium* have proven to be a prolific source of novel polyketide metabolites with pronounced biological activities.[2] Iriomoteolide 1a, a cytotoxic macrolide isolated from a marine dinoflagellate *Amphidinium* species (strain HYA024) collected off Iriomote Island, Japan, was first reported in 2007 by Tsuda et al.[3] The unique structure of iriomoteolide 1a (**1**, Scheme 1),[4] as determined by extensive NMR analysis, combined with its remarkably potent antiproliferative activity against various human cancer cell lines, has led to it becoming an attractive target for synthetic efforts and SAR studies to probe the pharmacophore and mechanism of action. To date, several groups have reported fragment syntheses and proposed coupling strategies towards iriomoteolide 1a.[5] As part of our interest in bioactive marine macrolides,[6] we initiated a programme towards developing a flexible and convergent total synthesis of iriomoteolide 1a (**1**). By exploiting our versatile lactate aldol methodology for stereocontrolled polyketide synthesis, we now report the construction of **2** and **3** as protected C13–C23 and C1–C9 segments of this important marine macrolide.

Iriomoteolide 1a (**1**) has a 23-carbon backbone and features a 20-membered macrolide, with an embedded six-membered hemiacetal ring, and has nine stereocentres and four isolated alkenes. As outlined in the retrosynthesis in Scheme 1, we envisaged the late-stage introduction of the labile hemiacetal ring by a suitable allylation to form the C12–C13 bond and a macrolactonisation engaging the C19 hydroxy, leading back to the C13–C23 aldehyde **2** and C1–C12 bromide **4**. The allylic bromide **4** should be



Scheme 1 Retrosynthetic analysis of iriomoteolide 1a (**1**) and key C13–C23 and C1–C9 segments **2** and **3**

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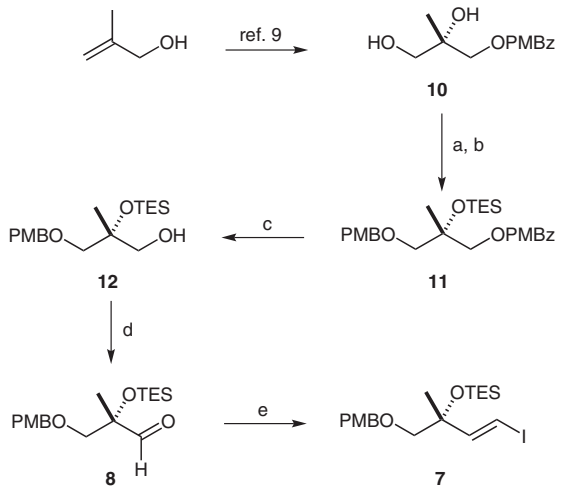
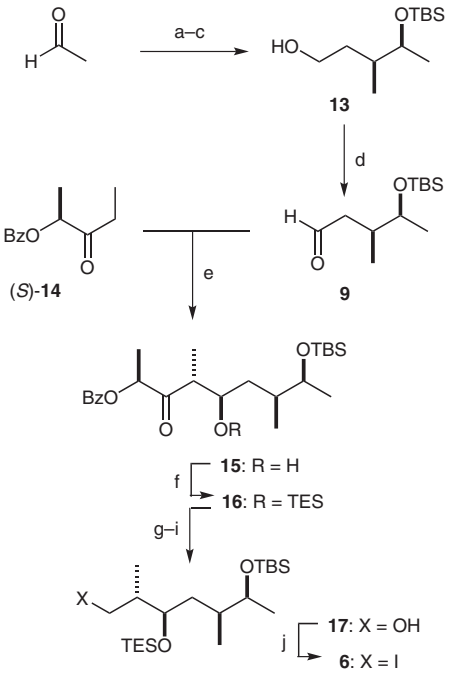
accessible in turn from elaboration of δ-lactone **3**, whose *Z*-configured trisubstituted olefin would be accessed through an intramolecular HWE reaction. The requisite C4–C5 *anti* relationship in its precursor **5** would then be installed by employing our boron-mediated lactate aldol reaction.[7] As the projected coupling partner for bromide **4**, aldehyde **2** would be formed through a Suzuki–Miyaura cross-coupling[8] of a borane derived from iodide **6** with vinyl iodide **7**, itself available from aldehyde **8**.[9] For the preparation of iodide **6**, a second lactate aldol reaction used in combination with Brown crotylation methodology was planned to configure the required C18–C19 *anti* and C21–C22 *syn* relationships, respectively.

Synthesis of the C13–C16 vinyl iodide **7** (Scheme 2) commenced with the enantioselective preparation of diol **10** from methallyl alcohol following the Sharpless dihydroxylation procedure reported by Corey.[9] Selective PMB ether formation on the primary alcohol in **10** (PMBTCA, CSA), followed by silylation of the tertiary alcohol (TESOTf), then provided the orthogonally protected triol **11** in 72% yield. Cleavage of the *para*-methoxybenzoyl (PMBz) ester with DIBAL-H and oxidation of the resulting primary alcohol **12** under Swern conditions cleanly afforded aldehyde **8** (90%). Finally, Takai olefination[10] with $CrCl_2$ and CHI_3 provided the targeted vinyl iodide **7** (82%) as a single geometric isomer.



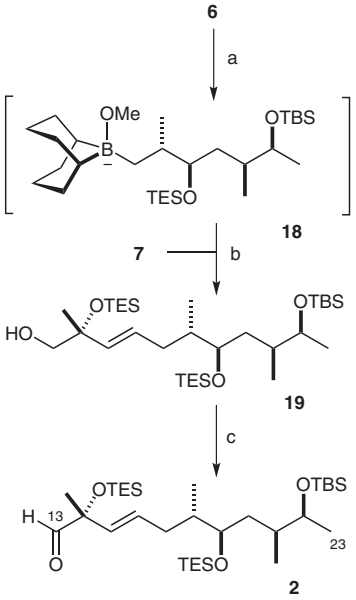
Scheme 2 Preparation of vinyl iodide **7**. *Reagents and conditions*: (a) PMBTCA, CSA, CH_2Cl_2, 73%; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 99%; (c) DIBAL-H, CH_2Cl_2, –78 °C, 93%; (d) oxalyl chloride, DMSO; Et_3N, CH_2Cl_2, –78 °C to 0 °C, 97%; (e) $CrCl_2$, CHI_3, THF, 82%.

The synthesis of the C17–C23 iodide partner **6** is shown in Scheme 3. Crotylation of acetaldehyde, performed under Brown's conditions using in situ generated (*Z*)-crotyldiisopinocampheylborane, followed by TBS protection of the resulting adduct, provided the corresponding *syn* homoallylic ether, with excellent stereocontrol (95% ee, 95:5 dr).[11] After hydroboration–oxidation of the olefin, alcohol **13** was isolated in 40% yield over the three steps from acetaldehyde. Oxidation with Dess–Martin periodinane afforded the aldehyde **9**, which was used crude for the subsequent boron aldol reaction. Based on our standard protocol,[7] enolisation of the ethyl ketone (*S*)-**14** [derived from ethyl (*S*)-lactate] with *c*-Hex_2BCl and Et_3N at 0 °C provided the corresponding *E*-enolate, which was treated with aldehyde **9** at –78 °C to afford the desired *anti*-configured aldol adduct **15** in 85% yield over two steps and with excellent stereocontrol (>97:3 dr). The newly formed alcohol was silylated (TESOTf) to provide **16** and the auxiliary cleaved using a three-step procedure involving $LiBH_4$ reduction of the ketone and the benzoate, oxidative cleavage of the ensuing diol with $Pb(OAc)_4$, followed by reduction with $NaBH_4$.[12] This provided the alcohol **17** in 87% yield. Finally, the targeted iodide **6** was accessed through treatment of **17** with I_2, PPh_3, and imidazole in THF (98%).

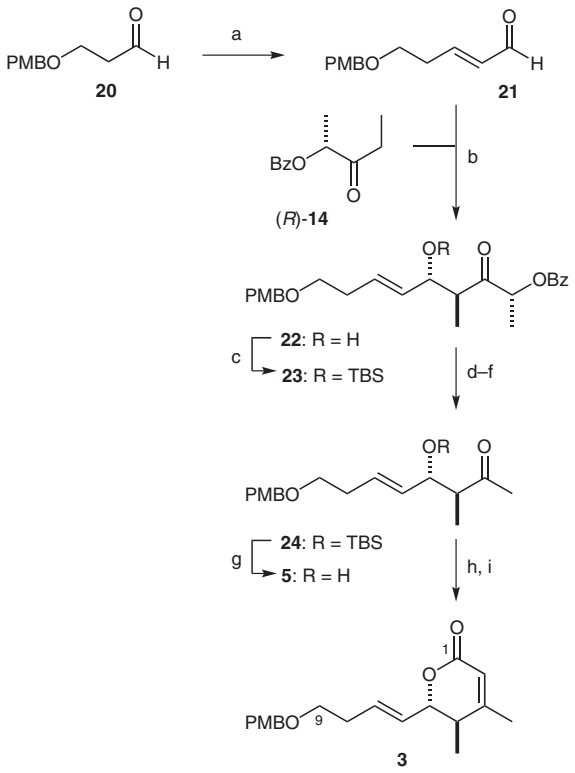


Scheme 3 Preparation of iodide **6**. *Reagents and conditions*: (a) KO*t*-Bu, *n*-BuLi, (+)-Ipc_2BOMe, *cis*-butene, THF, –78 °C; NaOH, H_2O_2; (b) TBSCl, imidazole, CH_2Cl_2; (c) $BH_3{\cdot}SMe_2$, THF, 0 °C; pH 7 buffer, H_2O_2, 40% over three steps; (d) DMP, $NaHCO_3$, CH_2Cl_2; (e) *c*-Hex_2BCl, Et_3N, Et_2O, 0 °C; **13**, –78 °C to –20 °C, Et_2O, 85% over two steps; (f) TESOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 99%; (g) $LiBH_4$, THF, 0 °C to r.t.; (h) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, 0 °C; (i) $NaBH_4$, EtOH, 0 °C, 87% over three steps; (j) I_2, Ph_3P, imidazole, 0 °C, THF, 98%.

With the two building blocks **6** and **7** now in hand, their cross-coupling was explored (Scheme 4). First, iodide **6** was converted into the boronate **18** through halogen–lithium exchange with *t*-BuLi and subsequent trapping with 9-BBNOMe. This intermediate boronate was then treated with vinyl iodide **7**, $AsPh_3$, Cs_2CO_3, and $Pd(dppf)Cl_2$ (7 mol%) in DMF–H_2O, which effected a smooth sp^2–sp^3 Suzuki–Miyaura coupling.[13] Following cleavage of the PMB ether with DDQ, the alcohol **19** was obtained in a pleasing 70% yield over the two steps. Finally, oxidation under Swern conditions gave the fully elaborated C13–



Scheme 4 Suzuki–Miyaura coupling of **6** and **7**. *Reagents and conditions*: (a) *t*-BuLi, 9-BBNOMe, Et_2O–THF, –78 °C to r.t.; **7**, $AsPh_3$, Cs_2CO_3, cat. Pd(dppf)Cl_2, DMF–H_2O; (b) DDQ, CH_2Cl_2–pH 7 buffer, 70% over two steps; (c) oxalyl chloride, DMSO, CH_2Cl_2, Et_3N, –78 °C to 0 °C, 95%.



Scheme 5 Completion of dihydropyrone **3**. *Reagents and conditions*: (a) Ph_3P=CHCHO, MeCN, 80 °C, 58%; (b) *c*-Hex_2BCl, Et_3N, Et_2O, 0 °C; **21**, –78 °C to –20 °C, Et_2O, 95%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 99%; (d) MeMgI, Et_2O, –78 °C to –10 °C; (e) DIBAL-H, CH_2Cl_2, –78 °C; (f) $NaIO_4$, MeOH–pH 7 buffer, 86% over three steps; (g) HF·pyridine, pyridine, THF, 92%; (h) $HO_2CCH_2PO(OEt)_2$, 2,4,6-trichlorobenzoyl chloride, Et_3N, 0 °C, PhMe; (i) $Ba(OH)_2$, THF–H_2O, 60%.

C23 segment **2** in 95% yield, corresponding to the northern hemisphere of iriomoteolide 1a.[14]

The synthesis of the C1–C9 segment **3** required for the southern hemisphere started with the aldehyde **20** (Scheme 5), which was submitted to a Wittig reaction with Ph_3P=CHCHO to afford the *E*-enal **21**. A second lactate aldol reaction, in this case using the enantiomeric ethyl ketone (*R*)-**14**, was now required to configure the C4 and C5 stereocentres of iriomoteolide. Under standard conditions,[7] this provided the desired *anti*-adduct **22** in 95% yield and with >97:3 dr.

The β-hydroxy ketone **22** was converted into the corresponding TBS ether **23**, then advanced to **24** via a three-step protocol. Initial MeMgI addition to the ketone was followed by scission of the benzoate with DIBAL-H and oxidative cleavage of the ensuing 1,2-diol using $NaIO_4$, which proceeded in 86% overall yield. This procedure proved higher yielding than attempted cleavage of the benzoate concomitant with ketone addition.[12] Removal of the TBS group (HF·pyridine, pyridine) then delivered the alcohol **5**. Finally, treatment of **5** with diethylphosphonoacetic acid generated the corresponding ester that underwent $Ba(OH)_2$-promoted HWE cyclisation[15] to give the dihydropyrone **3**,[16] incorporating the $\Delta^{2,3}$-alkene of iriomoteolide.

In summary, the stereocontrolled synthesis of the C13–C23 and C1–C9 segments **2** and **3** of the potent cytotoxic macrolide, iriomoteolide 1a, has been accomplished, featuring a combination of boron-mediated aldol reactions and a Suzuki–Miyaura cross-coupling to unite two fragments. Further work is currently under way to advancing these intermediates to achieve the total synthesis of iriomoteolide A.

Acknowledgment

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(14) Aldehyde **2**: $[\alpha]_D^{20}$ +32.0 (*c* 0.20, $CHCl_3$). IR (neat): 2952, 2881, 1737, 1461, 1376, 1252, 1095, 1011 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.33 (1 H, s), 5.72–5.78 (1 H, m), 5.32 (1 H, d, *J* = 15.4 Hz), 3.65–3.70 (2 H, m), 2.13–2.18 (1 H, m), 1.81–1.87 (1 H, m), 1.57–1.64 (2 H, m), 1.42–1.48 (2 H, m), 1.38 (3 H, s), 1.06 (3 H, d, *J* = 6.2 Hz), 0.96 (9 H, t, *J* = 7.8 Hz), 0.95 (9 H, t, *J* = 7.8 Hz), 0.88 (9 H, s), 0.86 (3 H, d, *J* = 7.1 Hz), 0.85 (3 H, d, *J* = 6.9 Hz), 0.62 (6 H, q, *J* = 7.8 Hz), 0.58 (6 H, q, *J* = 7.8 Hz), 0.04 (3 H, s), 0.02 (3 H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.7, 133.2, 130.8, 80.2, 74.6, 71.4, 37.6, 37.3, 36.3, 33.9, 25.9, 22.7. HRMS (ES^+): *m/z* calcd for $C_{32}H_{69}O_4Si_3$ [M + H^+] 601.4504; found: 601.4509.
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(16) Dihydropyrone **3**: $[\alpha]_D^{20}$ –30.0 (*c* 0.10, $CHCl_3$). IR (neat): 2931, 2856, 1709, 1512, 1249, 1095, 1034 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.24 (2 H, d, *J* = 8.6 Hz), 6.87 (2 H, d, *J* = 8.6 Hz), 5.79 (1 H, dt, *J* = 15.5, 6.8 Hz), 5.77 (1 H, s), 5.59 (1 H, ddt, *J* = 15.5, 7.2 Hz, 1.3 Hz), 4.52 (1 H, app t, *J* = 6.6 Hz), 4.41 (2 H, s), 3.80 (3 H, s), 3.42–3.47 (2 H, m), 2.36 (2 H, app qd, *J* = 6.7, 1.3 Hz), 2.26–2.33 (1 H, m), 1.94 (3 H, s), 1.15 (3 H, d, *J* = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.8, 160.4, 159.2, 132.8, 130.3, 129.2, 128.5, 116.3, 113.8, 83.2, 72.6, 68.9, 55.2, 37.6, 32.7, 21.4, 15.5. HRMS (ES^+): *m/z* calcd for $C_{19}H_{24}O_4Na$ [M + Na^+]: 339.1572; found: 339.1588.