Synthetic Studies towards Iriomoteolide-1a: Construction of the C13–C23 Fragment

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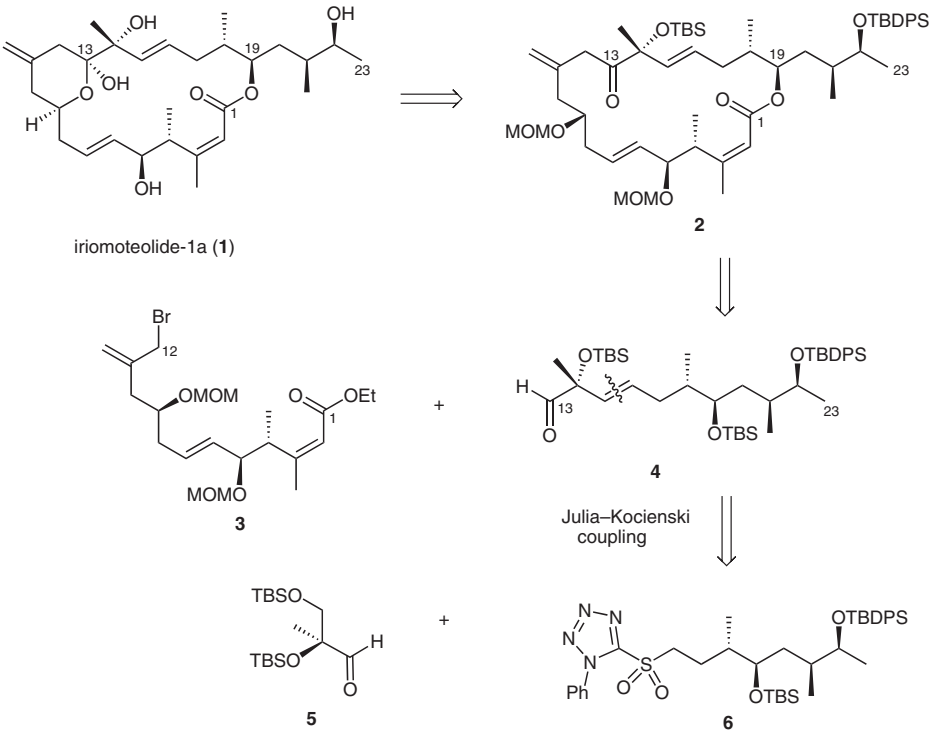
Abstract: A stereoselective synthesis of the C13–C23 segment of iriomoteolide-1a was achieved using, as key steps, a highly stereocontrolled crotylation to build the stereocenters at C18 and C19 and a Julia–Kocienski olefination to establish the C15–C16 *E*-olefin moiety.

Key words: iriomoteolide-1a, macrolide, dihydroxylation, crotylation, Julia–Kocienski olefination

Dinoflagellates have been reported to produce structurally unique metabolites with significant biological activities.[1]A series of macrolides known as amphidinolides have been isolated from *Dinoflagellate Amphidinium* species.[2] Owing to their potent cytotoxicity and intriguing structural features, these macrolides, as attractive targets, have inspired substantial synthetic studies.[3] For example, iriomoteolide-1a (**1**),[4] a 20-membered macrolide isolated from the *Amphidinium* species in 2007 by Tsuda and coworkers, has nine stereocenters, an acid-labile cyclic β,γ-unsaturated acetal unit, four hydroxyl groups and three endogenous double bonds, and exhibits extremely potent cytotoxicity IC_{50} values of 2 and 3 ng mL^{-1} against human B lymphocyte DG-75 cells and Epstein–Barr virus infected human B lymphocyte, respectively, although the mechanism of action still remains unknown.[4] Structural elucidation of iriomoteolide-1a was conducted by a combination of spectroscopic methods (ESI-HRMS, IR, and NMR) and a modified Mosher's protocol.[4]

Due to its significant biological activity and challenging structure, iriomoteolide-1a (**1**) has attracted great synthetic interests.[5] However, to the best of our knowledge, no total synthesis of **1** has been reported to date. As part of our ongoing studies directed toward the syntheses of various natural products of the amphidinolide family,[3d,6] we would like to herein present the assembly of the C13–C23 fragment **4** of iriomoteolide-1a. Our retrosynthetic analy-



Scheme 1 Retrosynthetic analysis of iriomoteolide-1a (**1**)

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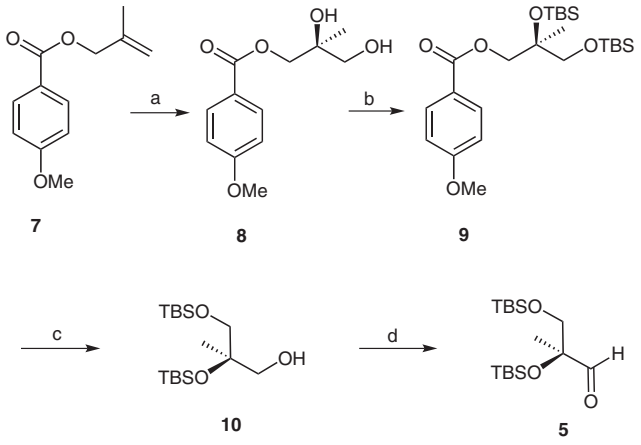


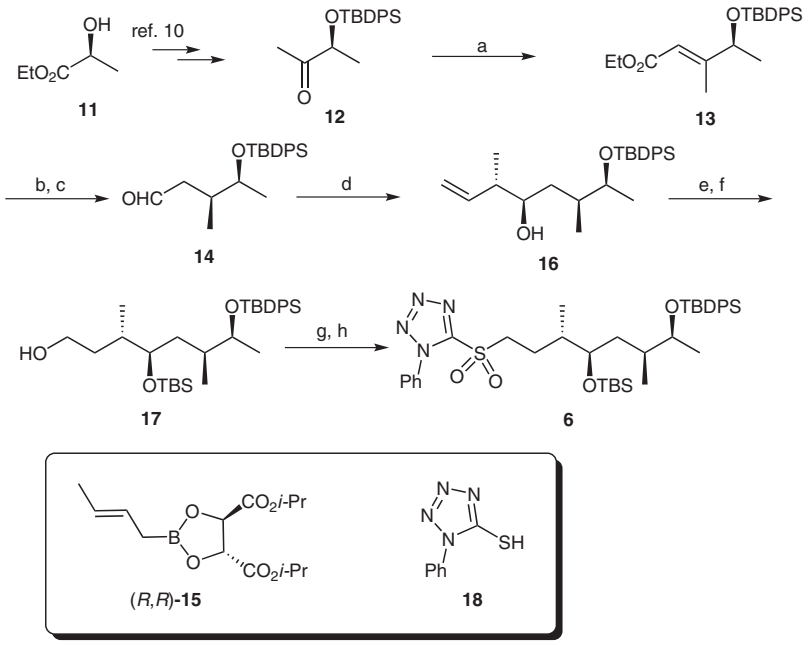
Scheme 2 *Reagents and conditions*: a) $(DHQ)_2PHAL$, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH–H_2O (1:1), 0 °C; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, r.t., 95% (two steps); c) DIBAL-H, toluene, –78 °C, 97%; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 96%.

sis of **1** is outlined in Scheme 1. We envisaged an access to the iriomoteolide-1a (**1**) from its precursor **2** through a late-stage intramolecular hemiacetalation. The C13–C23 segment (**4**), may be disconnected as a stereochermically elaborate aldehyde bearing five stereocenters, while the key *trans* double bond can be constructed by a Julia–Kocienski coupling between aldehyde **5** and sulfone **6**.[7]

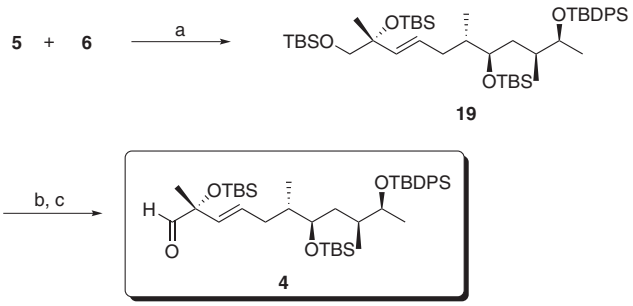
As shown in Scheme 2, aldehyde **5** possessing a chiral α-tertiary hydroxyl group could be prepared from olefin **7** as a starting material. Sharpless dihydroxylation[8] of **7** in the presence of AD-mix-β at 0 °C afforded in high enantioselectivity diol **8** (ee >95%), which in turn was protected with TBSOTf and 2,6-lutidine in CH_2Cl_2 to provide **9** in 95% yield over the two steps. Then the resulting silyl ether was reduced with diisobutylaluminum hydride (DIBAL-H) followed by Swern oxidation to provide aldehyde **5** (93% yield over the two steps), one of the two pieces for Julia–Kocienski reaction.[9]

The synthesis of sulfone segment **6** commenced from methyl ketone **12**,[10] a known intermediate easily preparable from commercially available (*S*)-(–)-ethyl lactate **11** (Scheme 3). Treatment of **12** with $(EtO)_2P(O)CH_2CO_2Et$ prepared in situ under standard Horner–Wadsworth–Emmons conditions provided the *E*-olefin **13** in 93% yield as a single product. Subsequently, stereoselective reduction of the double bond in **13** was called for to furnish the stereocenter at C21. After screening several conditions, the $NaBH_4/NiCl_2{\cdot}6H_2O$ system was found to be the best, affording the desired product with moderate selectivity (dr > 5:1).[11] The resulting ester was then reduced with DIBAL-H to give **14** in excellent yield over the two steps (85%). Next, asymmetric crotylation[12] of aldehyde **14** using the chiral *trans*-crotylboronate **15** (derived from L-diisopropyl tartrate) proceeded smoothly to give alcohol **16** in 98% yield with good diastereoselectivity (dr > 10:1) favoring the *anti*-isomer. Hydroxyl protection followed by hydroboration–oxidation yielded the primary alcohol **17**. Finally, conversion of **17** to Kocienski-type sulfone **6** was carried out smoothly by a two-step sequence including a Mitsunobu reaction[13] and an oxidation according to the literate procedures.[14]

With the two segments **5** and **6** in hand, we then investigated their coupling by the Julia–Kocienski reaction. As given in Scheme 4, the deprotonation of **6** with LHMDS in DMF–HMPA at –40 °C followed by treating with **5** led to the required *E*-isomer with excellent selectivity (dr > 20:1).[7,15] Finally, selective removal of a primary TBS



Scheme 3 *Reagents and conditions*: a) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, 0 °C; then **12**, r.t., 93%; b) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, –78 °C then r.t., 90%; c) DIBAL-H, CH_2Cl_2–toluene, –78 °C, 94%; d) **15**, 4 Å MS, toluene, –78 °C, 98%; e) TBSOTf, 2,6-lutidine, CH_2Cl_2, r.t., 100% f) $BH_3{\cdot}SMe_2$, THF, r.t.; then 2.5 M NaOH, 30% H_2O_2, r.t., 83%; g) **18**, DIAD, Ph_3P, THF, r.t., 96%; h) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, 30% H_2O_2, EtOH r.t., 97%.



Scheme 4 *Reagents and conditions*: a) **6**, LiHMDS, DMF–HMPA, –40 °C, 10 min; then **5**, warm to r.t., 50%; b) HF·py, pyridine, THF, r.t., 80%; c) TPAP, NMO, 4 Å MS, CH_2Cl_2, 90%.

group in **19** in the presence of HF·py and subsequent Ley oxidation afforded the desired aldehyde **4** in 72% yield over the two steps.[16]

In conclusion, we have developed a highly stereocontrolled synthesis of the C13–C23 segment **4** of iriomoteolide-1a in eleven steps and 21% overall yield in the longest linear sequence from methyl ketone **11** featuring a highly selective Julia–Kocienski coupling. Further investigations directed toward the total synthesis of iriomoteolide-1a are currently under way in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) Aldehyde **5**: $[\alpha]_D^{22}$ –6.4 (*c* 1.01, $CHCl_3$). IR (film): 2956, 2929, 2858, 1740, 1472, 1255, 1108, 837, 777 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.60 (s, 1 H), 3.66 (m, 2 H), 1.24 (s, 3 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.11 (s, 6 H), 0.03 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.5, 80.7, 68.4, 25.8, 25.7, 20.0, 18.2, 18.2, –2.6, –2.6, –5.6, –5.7. ESI-MS: *m/z* = 387.2 $[M + MeOH + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{16}H_{36}O_3Si_2Na^+$ $[M + Na]^+$: 355.2108; found: 355.2095.

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(14) Sulfone **6**: $[\alpha]_D^{24}$ –21.4 (*c* 1.62, $CHCl_3$). IR (film): 3077, 2957, 2929, 2857, 1593, 1498, 1463, 1428, 1379, 1342, 1256, 1153, 1110, 1078, 1035, 951, 835, 774 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.66 (m, 6 H), 7.61 (m, 3 H), 7.42–7.35 (m, 6 H), 3.95–3.88 (m, 1 H), 3.80–3.77 (m, 1 H), 3.68–3.56 (m, 2 H), 1.99–1.93 (m, 1 H), 1.87–1.82 (m, 1 H), 1.72–1.64 (m, 2 H), 1.45 (m, 1 H), 1.37–1.30 (m, 1 H), 1.03 (s, 9 H), 1.00 (d, *J* = 7.5 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.87 (s, 9 H), 0.01 (s, 3 H), –0.02 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4, 135.9, 135.9, 134.9, 134.0, 133.1, 131.3, 129.6, 129.6, 129.4, 127.6, 127.3, 125.0, 74.5, 72.5, 54.4, 37.0, 36.8, 35.4, 27.0, 25.9, 22.6, 20.3, 19.3, 18.0, 16.1, 14.6, –4.3, –4.5. ESI-MS: *m/z* = 757.2 $[M + Na]^+$. HRMS (MALDI): *m/z* calcd for $C_{39}H_{58}N_4O_4Si_2SNa^+$ $[M + Na]^+$: 757.3633; found: 757.3610.

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(16) Aldehyde **4**: $[\alpha]_D^{24}$ –22.6 (*c* 0.66, $CHCl_3$). IR (film): 3584, 3072, 3050, 2956, 2930, 2893, 2858, 1472, 1463, 1428,

1378, 1361, 1255, 1110, 1029, 975, 938, 835, 739, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.33 (s, 1 H), 7.69–7.66 (m, 4 H), 7.43–7.35 (m, 6 H), 5.76–5.70 (m, 1 H), 5.26 (d, *J* = 15.6 Hz, 1 H), 3.79–3.77 (m, 1 H), 3.58–3. 56 (m, 1 H), 2.10–2.04 (m, 1 H), 1.81–1.75 (m, 1 H), 1.72–1.67 (m, 1 H), 1.57–1.50 (m, 2 H), 1.37 (s, 3 H), 1.26–1.20 (m, 1 H), 1.06 (s, 9 H), 0.96 (d, *J* = 6.0 Hz, 3 H), 0.93 (s, 9 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.85 (d, *J* = 6.9 Hz, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H), –0.00 (s, 3 H), –0.02 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.9, 135.9, 135.1, 135.0, 134.2, 130.1, 29.5, 129.4, 127.5, 127.3, 75.7, 74.8, 72.6, 71.4, 37.7, 37.0, 35.8, 34.1, 27.1, 25.9, 25.8, 23.6, 19.9, 19.4, 18.1, 15.8, 15.2, –2.3, –4.3, –4.4. ESI-MS: *m/z* = 749.4 $[M + Na]^+$. HRMS (MALDI): *m/z* calcd for $C_{42}H_{74}O_4Si_3Na^+$ $[M + Na]^+$: 749.4803; found: 749.4787.