Tetrahedron Letters 50 (2009) 4485–4487

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective synthesis of iriomoteolide-1a hemiketal core

Jun Xie, David A. Horne *

Department of Molecular Medicine, Beckman Research Institute and Graduate School of Biological Sciences at City of Hope, Duarte, CA 91010, USA

ARTICLE INFO

Article history:
Received 21 March 2009
Revised 13 May 2009
Accepted 18 May 2009
Available online 29 May 2009

ABSTRACT

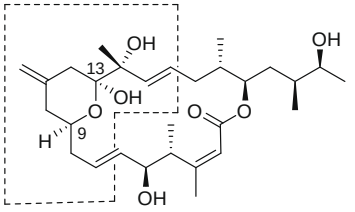
A stereoselective synthesis of the cyclic hemiketal core of iriometeolide-1a (**1**) is described. The key step involves a Sakurai reaction of allylsilane **4** and aldehyde **5**, which bears a chiral α-tertiary center. Mild TES deprotection of β,γ-unsaturated ketone **23** led to concomitant cyclization to produce the fully intact hemiketal core **2**.

In 2007, Tsuda's group reported the isolation and structure determination of the remarkably potent cytotoxic 20-membered ring macrolide, iriomoteolide-1a (**1**) from the *Amphidinium* sp. strain HYA024.[1] IC_{50} values against human B lymphocyte DG-75 cells and Epstein-Barr virus infected human B lymphocyte Raji cells were measured at 2 and 3 ng/mL, respectively. The structure of **1** was elucidated primarily by 2-D NMR analysis. Contained within this natural product is a cyclic hemiketal core that bears an exocyclic methylene unit and a tertiary chiral center that is vicinal to the hemiketal functionality. These distinguishing structural features make this system unique among related systems, such as the one found in amphidinolide-P.[2]

Recently, papers have begun to emerge that describe various synthetic efforts toward **1** but none have reported the synthesis of the fully intact six-membered ring hemiketal core.[3] Herein, we describe a relatively short stereoselective synthesis of core structure **2** which bears all the essential structural elements found in the natural product. These include the six-membered hemiketal ring possessing the exocyclic methylene unit as well as the adjacent chiral tertiary allylic alcohol appendage.

The retrosynthesis of **2** is depicted in Figure 1. A key step in the synthetic scheme centers on a Sakurai reaction[4] between an allylsilane and aldehyde that bears an α-chiral tertiary center. While this work was in progress, a strategically similar approach outlined by Ghosh has appeared.[3b] Subsequent oxidation of the resulting alcohol and deprotection facilitates concomitant cyclization to the desired hemiketal functionality.

Preparation of allylsilane **3** commenced with ring opening of epoxide **7**[5] with commercially available **6** in the presence of *t*-BuLi and CuI to provide allylsilane **8** in excellent yield.[6] The resulting alcohol was protected with either TBS or TES to generate coupling precursors **3** and **4**, respectively (Scheme 1).



iriomoteolide-1a (**1**)

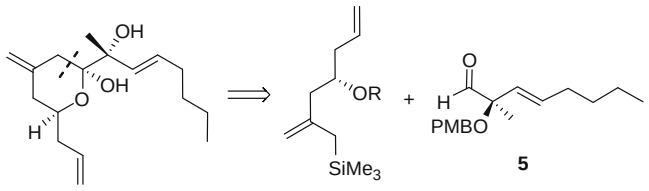
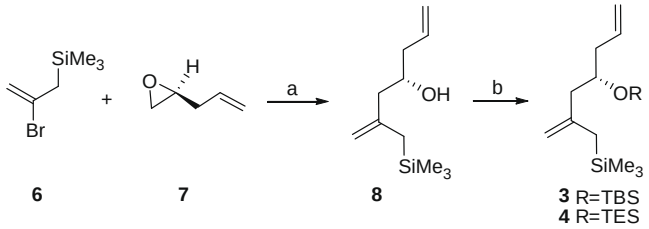


Figure 1. Retrosynthetic analysis of core structure **2**.



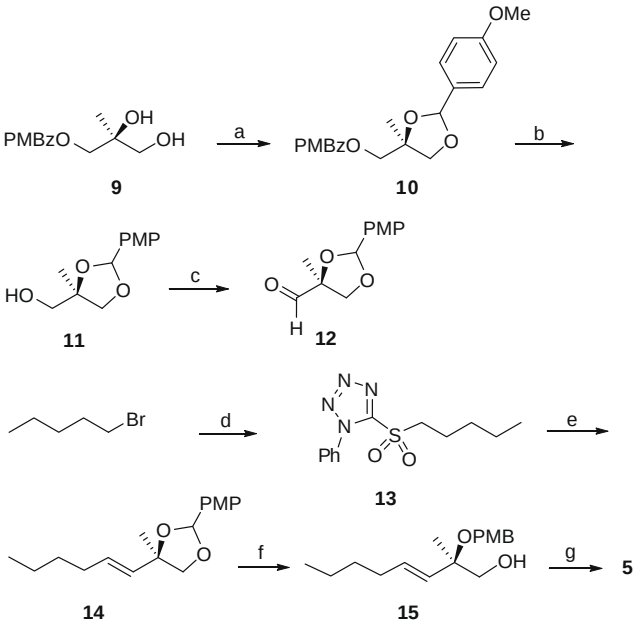
Scheme 1. Synthesis of allyltrimethylsilanes **3** and **4**. Reagents and conditions: (a) **6**, *t*-BuLi, CuI, −78 °C then **7**, −45 °C, 84%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 99% or TESOTf, 2,6-lutidine, CH_2Cl_2, 91%.

* Corresponding author. Tel.: +1 626 256 4673; fax: +1 626 930 5410.
E-mail address: dhorne@coh.org (D.A. Horne).

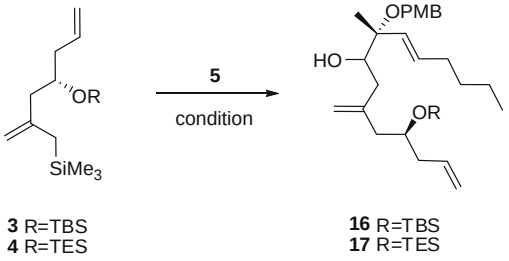
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.05.092

The preparation of aldehyde **5** began with known diol **9**[7], which was protected as its PMP acetal to afford **10** (Scheme 2). Cleavage of the PMBz ester with MeONa followed by Dess–Martin periodinane oxidation of the resulting alcohol gave aldehyde **12,** which was used in the next step without chromatographic purification. In our model study, sulfone **13** was prepared from 1-bromopentane and utilized in a Julia-Kocienski olefination[8] with aldehyde **12**. The sole *E*-olefin **14** was obtained in 78% yield for the two steps. Treatment of **14** with DIBAL-H yielded primary alcohol **15**. Oxidation of this alcohol with Dess–Martin periodinane furnished coupling precursor **5,** which was used directly in the next step.

With allyltrimethylsilane **3** and aldehyde **5** in hand, several Lewis acids were explored in the Sakurai reaction (Scheme 3). Using $TiCl_4$, only trace amounts of product were observed. On the other hand, when $SnCl_4$ was utilized, alcohol **16**[9] was produced as a single diastereomer in 30% yield over two steps. The stereochemistry of the newly formed chiral center was not determined at this time since the chirality at this center disappears upon subsequent oxidization to the ketone. Using $BF_3{\cdot}Et_2O$, the allylation yield was slightly improved to 37% overall but a different stereoisomer at the alcohol center is produced. While awaiting confirmation, the allylation products from the use of $SnCl_4$ and $BF_3{\cdot}Et_2O$ are anticipated to result from chelation controlled and Felkin-Ahn type selectivities, respectively. As expected, similar results were seen with TBS or TES protected alcohols. The intermolecular addition of an allylsilane to a relatively hindered aldehyde bearing an α-chiral tertiary center represents a new example that expands the scope of the Sakurai reaction.



Scheme 2. Synthesis of aldehyde **5**. *Abbreviations*: PMBz = *p*-methoxybenzoyl; PMP = *p*-methoxyphenyl; PMB = *p*-methoxybenzyl. Reagents and conditions: (a) 4-methoxybenzaldehyde dimethyl acetal, PPTS (cat), CH_2Cl_2, 76%; (b) NaOMe, MeOH, 95%; (c) Dess–Martin, $NaHCO_3$, CH_2Cl_2; (d) (i) Na_2CO_3, acetone, reflux; (ii) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, 95% for 2 steps; (e) **13**, KHMDS, −78 °C then **12** to rt, 79% from **11**; (f) DIBAL-H, −78 °C, CH_2Cl_2, 82%; (g) Dess–Martin, $NaHCO_3$, CH_2Cl_2.



3 R=TBS
4 R=TES

16 R=TBS
17 R=TES

	Lewis Acid	Yield
R=TBS	$TiCl_4$	trace
R=TBS	$SnCl_4$	30% from **15**
R=TBS	$BF_3{\cdot}Et_2O$	37% from **15**

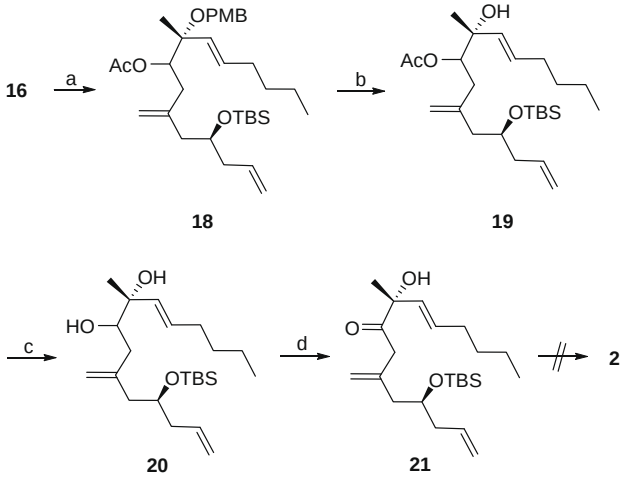
Scheme 3. Sakurai reaction.

At this stage, we chose to delay oxidation of alcohols **16**/**17** over concerns regarding a potentially undesirable double bond migration in subsequent steps yielding the corresponding α,β-unsaturated ketone. Additional concerns regarding vicinal hydroxyl participation upon deprotection of the PMB moiety of **16** led us to protect the newly formed hydroxyl group in **16** with AcCl to give **18**. Removal of the PMB group proceeded smoothly by DDQ oxidation (Scheme 4). Cleavage of the acetyl group using $LiAlH_4$ produced diol **20** in nearly quantitative yield. The desired β,γ-unsaturated ketone **21**[10] was obtained in excellent yield upon oxidation of alcohol **20** with $SO_3{\cdot}Py$.

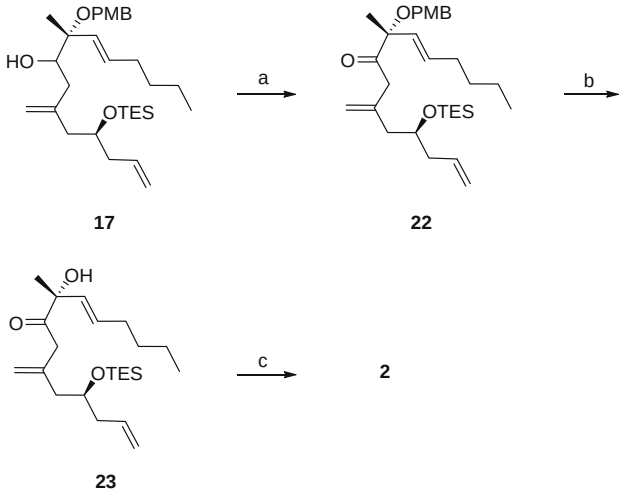
With cyclization precursor **21** in hand, all that remained was deprotection of the TBS group and cyclization. Several conditions were attempted which had previously proven successful in related systems.[11] These included TBAF, TBAF plus HOAc, TASF (tris(dimethylamino)sulfonium difluorotrimethylsilicate), and TBAT (tetrabutylammonium triphenyldifluorosilicate), but in our case, no cyclization products were obtained. Only double bond migration of β,γ-unsaturated ketone **21** to the corresponding α,β-unsaturated system was observed. When HF·Py was tried, however, an interesting observation was noted. Neither cyclization nor isomerization products were detected. The bulk of the reaction mixture comprised unreacted starting material. This suggests that the β,γ-enone system of **21** is stable to HF·Py and replacing the TBS group with the more labile TES moiety might facilitate deprotection and cyclization.

Thus, allylsilane **8** was retooled as its TES ether by treatment with TESOTf, which afforded **4**. Addition of allylsilane **4** to aldehyde **5** occurred in the presence of $BF_3{\cdot}Et_2O$ to provide compound **17** in 34% over two steps.

Dess–Martin periodinane oxidation of homoallylic alcohol **17** produced β,γ-unsaturated ketone **22** (Scheme 5). Selective removal



Scheme 4. Attempted synthesis of core structure **2**. Reagents: (a) AcCl, Py, CH_2Cl_2, 88%; (b) DDQ, CH_2Cl_2: pH 7 buffer = 1:1, 83%; (c) $LiAlH_4$, THF, 99%; (d) $SO_3{\cdot}Py$, *i*-Pr_2NEt, DMSO, CH_2Cl_2, 99%.



Scheme 5. Synthesis of the core structure **2**. Reagents: (a) Dess–Martin, $NaHCO_3$, CH_2Cl_2, 99%; (b) DDQ, CH_2Cl_2: pH 7 buffer = 1:1, 90% (c) HF·Py, Py, THF, 74%.

of the PMB ether group without enone migration was accomplished by treatment of **22** with DDQ in a 1:1 mixture of CH_2Cl_2 and pH 7 buffer. This resulted in the generation of ketone **23** in excellent yield. Finally, deprotection of the TES group by HF·Py led to concomitant cyclization to afford the desired product **2**[12] as a single stereoisomer. Positive ROSEY interactions seen between H9 and OH13 support the configuration of the newly form stereocenter as indicated.

Cyclic ketal **2** was examined for cytotoxic activity against melanoma (A2058) and prostate (DU145) cell lines. At the highest dose examined (20 μM), viability (as measured by MTS assay) in both cell lines was approximately 70% of the control. These results indicate that the cyclic hemiketal alone is not responsible for the remarkable cytotoxicity observed in the natural product.

In summary, the synthesis of the six-membered ring hemiketal core of iriomoteolide-1a (**1**) has been achieved in a relatively efficient manner. Noteworthy is the application of the Sakurai reaction involving an aldehyde bearing an α-chiral tertiary center. Furthermore, the use of TES/HF·Py for the protection/deprotection sequence was found to be a viable solution for cyclization and hemiketal formation.

Acknowledgments

The authors thank Dr. Sangkil Nam for cytotoxicity testing. Support from Chugai Pharmaceutical Co. and the Caltech/City of Hope Medical Research Fund is gratefully acknowledged. The authors thank Professor Brian Stoltz (Caltech) for helpful discussions.

References and notes

1. Tsuda, M.; Oguchi, K.; Iwamoto, R.; Okamoto, Y.; Kobayashi, J.; Fukushi, E.; Kawabata, J.; Ozawa, T.; Masuda, A.; Kitay, Y.; Omasa, K. *J. Org. Chem.* **2007**, *72*, 4469.
2. Ishibashi, M.; Takahashi, M.; Kobayashi, J. *J. Org. Chem.* **1995**, *60*, 6062.
3. (a) Fang, L.; Xue, H.; Yang, J. *Org. Lett.* **2008**, *10*, 4645; (b) Ghosh, A. K.; Yuan, H. *Tetrahedron Lett.* **2009**, *50*, 1416.
4. Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *17*, 1295.
5. Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2004**, *126*, 2495.
6. (a) Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. *Proc. Natl. Acad. Sci.* **2004**, *101*, 12058; (b) Munoz-Torrero, D.; Brückner, R. *Eur. J. Org. Chem.* **1998**, *1998*, 1031.
7. Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805.
8. (a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26; (b) Hayes, P. Y.; Kitching, W. *J. Am. Chem. Soc.* **2002**, *124*, 9718.
9. Compound **16**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, 2H, J = 8.6 Hz), 6.85 (d, 2H, J = 8.6 Hz), 5.78–5.85 (m, 1H), 5.70 (dt, 1H, J = 16 Hz, 6.4 Hz), 5.59 (d, 1H, J = 16 Hz), 4.99–5.03 (m, 2H), 4.91 (s, 1H), 4.86 (s, 1H), 4.28–4.34 (m, 2H), 3.81–3.85 (m, 1H), 3.79 (s, 3H), 3.63–3.66 (m, 1H), 2.53 (d, 1H, J = 1.9 Hz), 1.98–2.28 (m, 8H), 1.24–1.42 (m, 4H), 1.32 (s, 3H), 0.90 (t, 3H, J = 7 Hz), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 159.1, 144.4, 135.6, 134.7, 131.8, 130.8, 129.1, 117.1, 114.7, 113.9, 80.4, 75.9, 71.1, 64.4, 55.5, 43.8, 41.6, 38.5, 32.6, 31.8, 26.1, 22.5, 18.4, 18.2, 14.2, −4.2, −4.3; HRMS (EI) calcd for $[M+H^+-H_2O]$: 499.3608; found 499.3627.
10. Compound **21**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74–5.90 (m, 2H), 5.50 (d, 1H, J = 15.5 Hz), 5.01–5.06 (m, 2H), 5.00 (s, 1H), 4.89 (s, 1H), 3.94 (s, 1H), 3.77–3.83 (m, 1H), 3.26–3.36 (m, 2H), 2.04–2.26 (m, 6H), 1.45 (s, 3H), 1.28–1.41 (m, 4H), 0.89 (t, 3H, J = 7 Hz), 0.87 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 210.1, 139.9, 135.0, 133.5, 130.7, 117.5, 117.4, 79.2, 71.3, 43.8, 43.4, 41.9, 32.2, 31.3, 26.1, 24.8, 22.5, 18.3, 14.1, −4.2, −4.3; HRMS (EI) calcd for $[M+H^+]$: 395.2982; found 395.2971.
11. (a) Williams, D. R.; Myers, B. J.; Mi, L. *Org. Lett.* **2000**, *2*, 945; (b) Savall, B. M.; Blanchard, N.; Roush, W. R. *Org. Lett.* **2003**, *5*, 377; (c) Trost, B. M.; Yang, H.; Probst, G. D. *J. Am. Chem. Soc.* **2004**, *126*, 48; (d) Breitfelder, S.; Schuemacher, A. C.; Rolle, T.; Kikuchi, M.; Hoffmann, R. W. *Helv. Chim. Acta* **2004**, *87*, 1202.
12. Compound **2**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.66–5.84 (m, 3H), 5.04–5.10 (m, 2H), 4.86 (s, 1H), 4.83 (s, 1H), 3.88–3.94 (m, 1H), 3.03 (s, 1H), 2.37 (s, 1H), 2.22–2.32 (m, 5H), 2.05–2.10 (m, 2H), 1.86–1.93 (m, 1H), 1.33–1.47 (m, 4H), 1.30 (s, 3H), 0.90 (t, 3H, J = 7.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 141.9, 134.7, 132.3, 131.3, 117.3, 111.4, 99.4, 77.3, 70.7, 40.4, 39.5, 37.9, 32.4, 31.6, 22.4, 21.0, 14.1; HRMS (EI) calcd for $[M+H^+-H_2O]$: 263.2011; found 263.2020.