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Synthesis of the C_{17}–C_{25} subunit of lasonolide A utilizing a Tsuchihashi–Yamamoto type rearrangement

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Abstract—An efficient synthesis of the C_{17}–C_{25} subunit resident in (−)-lasonolide A is reported herein. The key reaction features that were utilized include a Tsuchihashi–Yamamoto type rearrangement and Molander–Reformatsky SmI_2 mediated intramolecular aldol reaction sequence. Lastly, a diastereoselective target oriented β-*C*-glycoside formation sequence via an oxocarbenium reduction completed the stereochemistry required for the completion of the C_{17}–C_{25} segment of (−)-lasonolide A.

The construction of α-and β-*C*-glycosides has become increasingly important in the synthesis of biologically active natural products. Consequently, there has been substantial growth in the arena of new synthetic methodologies within this area. Along this line, building blocks have been synthesized by using several innovative technologies including the hetero-atom Diels–Alder reaction,[1] Petasis–Ferrier rearrangement,[2] intermolecular silyl-modified Sakurai and Prins cyclizations,[3] *exo*-Pd-mediated allylic etherification,[4] radical cyclization,[5] and intramolecular Michael additions with oxygen nucleophiles.[6] As a complementary procedure to these technologies, our research program is interested in expanding and concomitantly defining a broader scope of Kishi's strategy for the synthesis of β-*C*-glycosides.[7]

First isolated from *Forcepia* sp. in 1994 by McConnell, (−)-lasonolide A (**1**) represents a potent anti-tumor agent, which exhibits significant cytotoxic activity (ng/ml) against P388 murine leukemia, A-549 human lung carcinoma cell lines, and inhibits cell adhesion in the EL-4.IL-2 cell line.[8] In addition to the impressive levels of biological activity, the highly unique structure of **1** makes it an attractive target for total synthesis and an ideal target for testing synthetic methodologies of β-*C*-glycosides. Thus, a variety of synthetic approaches to **1** have been reported[9] with four total syntheses reported to date.[5,10] Lee and co-workers were the first to disclose the asymmetric total synthesis of **1**, in addition to a structural revision, thus determining both the relative and absolute configuration of natural (−)-lasonolide.[5] Key steps in their synthesis included two radical cyclizations to form both β-*C*-glycoside units followed by a Yamaguchi macrocyclization. Subsequently, Kang reported the second total synthesis of **1**, by utilizing an efficient desymmetrization followed by an asymmetric allylation en route to the completion of the upper β-*C*-glycoside subunit and then ultimately **1**. In addition, the Shishido and Ghosh groups have also recently completed the total synthesis of **1**.[10]

As delineated in Scheme 1, our initial approach to the synthesis of the C_{17}–C_{25} portion of **1** was based on a stereoselective reduction of a cyclic oxocarbenium cation mediated by the treatment of an appropriate hemiketal with Lewis or protic acid. In turn, the hemi-ketal was envisaged to be derived from a nucleophilic addition of the allyl Grignard reagent to the corresponding lactone **3**. We envisioned a SmI_2 Molander–Reformatsky[11] lactonization sequence for the synthesis of **3**, which would be derived from β-hydroxy aldehyde **4**. Finally, the quaternary center resident in **4** was envisioned via a Tsuchihashi–Yamamoto type rearrangement by means of an appropriate chiral vinyl epoxide.[12]

The synthesis of **2** was initiated with the previously reported benzyl protected aldehyde **5**,[13] as shown in Scheme 2. Thus, a stabilized Wittig olefination of the aldehyde moiety of **5** with the commercially available carbethoxymethylene phosphorane selectively provided

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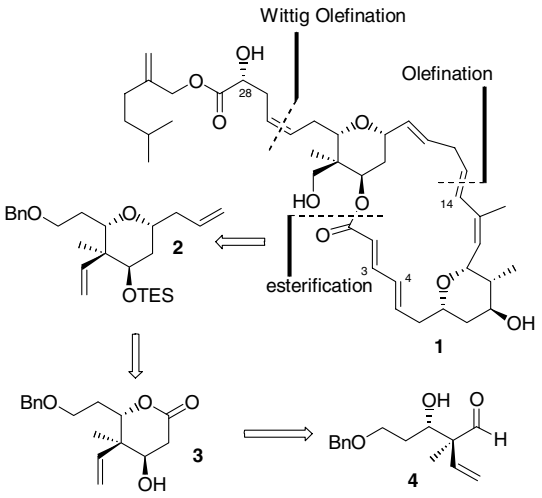
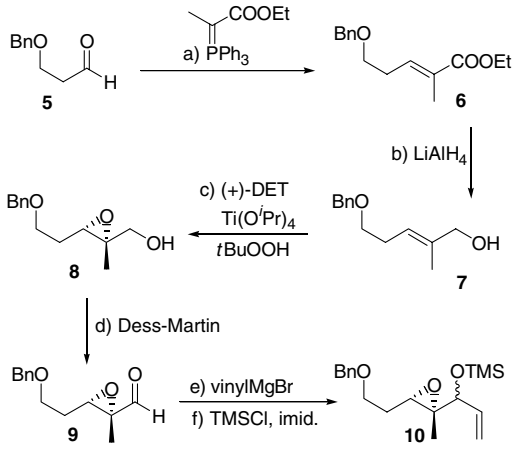
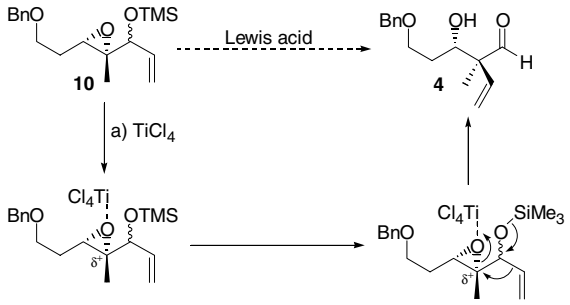


Scheme 1. Retrosynthesis of (−)-lasonolide A.



Scheme 2. Synthesis of epoxy intermediate **10**. Reagents and conditions: (a) (carbethoxymethylene)triphenylphosphorane (1.2 equiv), CH_2Cl_2, rt, 12 h, 84%. (b) $LiAlH_4$ (1.1 equiv), Et_2O, rt, 20 h, 90%. (c) (+)-Diethyl tartrate (1.2 equiv), $Ti(O^iPr)_4$ (1.1 equiv), *t*BuOOH (2.0 equiv), CH_2Cl_2, 0 °C, 6 h, 77%. (d) Dess–Martin periodinane (1.5 equiv), CH_2Cl_2, rt, 2 h, 85%. (e) VinylMgBr (2.0 equiv), THF, −20 °C, 1 h, 78%. (f) TMSCl (2.0 equiv), imid. (4.0 equiv), DMF, rt, 6 h, 82%. Dess–Martin periodinane = 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxo-3-(1*H*)-one; imid. = imidazole.

the (*E*)-α,β-unsaturated ethyl ester **6** in 84% yield. Ensuing reduction of **6** with $LiAlH_4$ readily furnished the allylic alcohol **7** in 90% yield and set the stage for the introduction of the initial chirality required for the completion of **2**. Along this line, Sharpless' asymmetric epoxidation[14] of the olefin moiety resident in alcohol **7** with the obligatory reagents (diethyl tartrate, $Ti(OiPr)_4$, and *t*BuOOH) afforded epoxy alcohol **8** in 77% yield with an er of 96:4 as checked via the Mosher ester. Subsequent oxidation of the primary hydroxyl group with Dess–Martin periodinane provided the epoxy aldehyde **9**, which was immediately transformed to the vinyl alcohol as a mixture of inconsequential diastereomers by means of nucleophilic addition of the vinyl Grignard reagent. Final protection of the free hydroxyl moiety as a silyl ether was accomplished with TMSCl and imidazole



Scheme 3. Synthesis of β-hydroxy aldehyde **4**. Reagents and conditions: (a) $TiCl_4$ (1.5 equiv, 1 M soln), CH_2Cl_2, −78 °C, 1 h, 78%.

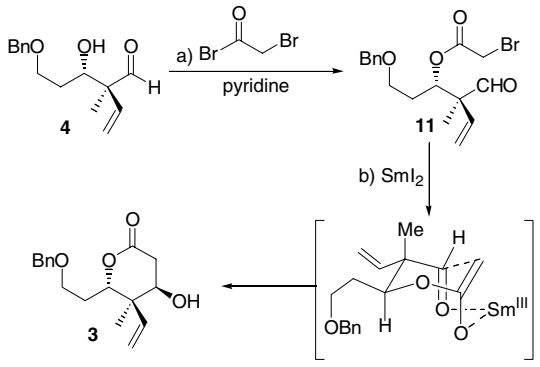
to furnish **10** with a combined yield of 54% over three steps from epoxy alcohol **8**. With vinyl epoxide **10** in hand, we turned our attention to the Tsuchihashi–Yamamoto rearrangement as the means for the introduction of the required chiral quaternary center of the upper β-*C*-glycoside unit of **1**.

As shown in Scheme 3, we envisioned that treatment of **10** with a Lewis acid would trigger a 1,2 vinyl migration and proceed to provide the requisite β-hydroxy aldehyde as reported by Tsuchihashi and Yamamoto.[12] With this in mind, addition of a 1 M solution of $TiCl_4$ to the vinyl epoxy intermediate **10** did indeed elicit the proposed 1,2-vinyl migration and provided the desired β-hydroxy aldehyde **4** in 78% yield with a 15:1 dr as determined by ^1H NMR.[15]

With **4** in hand, the stage was set for the intramolecular SmI_2 mediated Reformatsky sequence. Molander reported that the treatment of a bromoacetyl moiety with SmI_2 readily allowed for the synthesis of a Sm(III) enolate, which subsequently underwent an intramolecular aldol reaction with a pendent aldehyde via a double six membered transition state to furnish selectively a β-hydroxy lactone with exceptional diastereoselectivity.[11]

In order to investigate the feasibility of this reaction, we transformed β-hydroxy aldehyde **4** into bromoester **11** in an acceptable 82% yield. As anticipated, treatment of **11** with SmI_2 provided the initial Sm(III) enolate intermediate, which quickly underwent cyclization to provide lactone **3** as a single diastereomer as observed by ^1H NMR in 83% yield via the proposed transition state as shown in Scheme 4.[16] Two observations are worth noting. The first is that the α-chiral quaternary center had little to no influence on the stereochemical outcome of the Molander–Reformatsky reaction. Secondly, the inclusion of the α-chiral quaternary center provided a greater yield (83%) than that of a lesser substituted β-bromoacetate aldehyde, via the presumed Thorpe–Ingold effect during cyclization.[17]

With the key hydroxy-lactone **3** in hand, our attention was initially focused on the allyl β-*C*-glycoside formation followed by the final elaboration of the terminal alkene functional group into the final targeted structure **14**. Thus, treatment of lactone **3** with excess allyl magnesium bromide readily afforded the lactol intermediate as



Scheme 4. Synthesis of lactone **3**. Reagents and conditions: (a) bromoacetyl-bromide (2.0 equiv), pyridine (3.0 equiv), CH_2Cl_2, 0 °C, 2 h, 82%. (b) SmI_2 (2.5 equiv), THF, 0 °C, 1.5 h, 83%.

a mixture of two diastereomers as observed by ^1H NMR. Immediate addition of TFA seemingly provided the oxocarbenium intermediate **15**, which was subsequently reduced with Et_3SiH. As observed in our previous syntheses of (−)-dactylolide and diospongin A,[7c,d] the free secondary hydroxyl group was concomitantly protected as a TES ether under the reductive conditions for the transformation of **3** to **2** via a proposed pentavalent siliconate intermediate. The overall yield of the four transformations (nucleophilic addition, oxocarbenium formation, active silylating reagent formation via the proposed siliconate, and concomitant intramolecular reduction of the oxocarbenium cation) was a very respectable 66%.[18] The global stereochemistry of the β-*C*-glycoside intermediate **2** was deduced via the NOE enhancements as shown in Figure 1. Oxidation of both terminal olefins via O_3, followed by an aqueous acid workup, provided the deprotected bis-aldehyde compound **12** in 95% yield. Final global reduction of the bis-aldehyde moieties resident in **12** to triol **13** and ensuing acetonide formation of the *syn*-1,3 diol with DMP and PPTS readily proceeded and furnished intermediate **14** in 59% yield over two steps from **12** Scheme 5.

In conclusion, we have completed an efficient synthesis of the C_{17}–C_{25} subunit resident in (−)-lasonolide A. The key reaction features that were utilized include a Tsuchihashi–Yamamoto type rearrangement and Molander–Reformatsky SmI_2 mediated intramolecular aldol reaction sequence. Lastly, a diastereoselective target oriented β-*C*-glycoside formation sequence via an axial oxocarbenium reduction completed the stereochemistry required for the completion of the C_{17}–C_{25} segment of (−)-lasonolide A. Studies toward the total synthesis of **1** are ongoing and will be reported in due course.

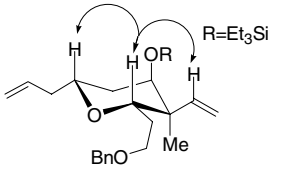
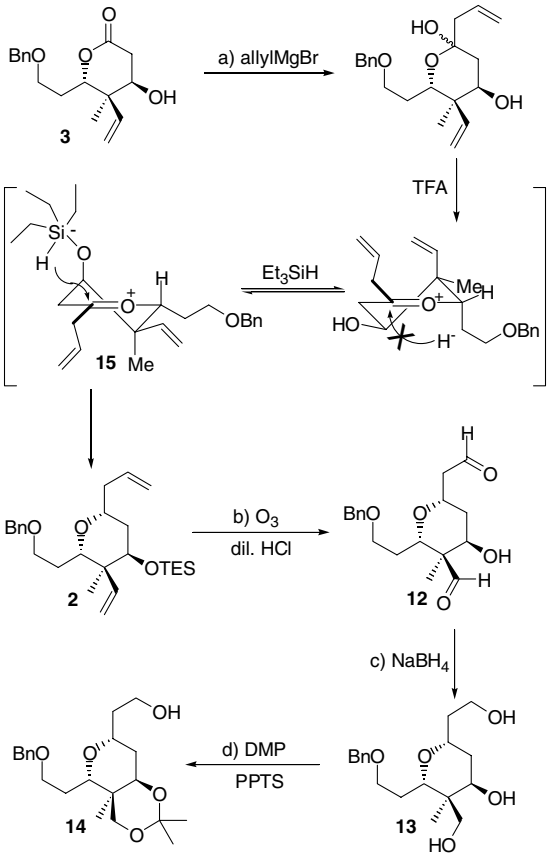


Figure 1. Key NOE enhancements of intermediate **2**.



Scheme 5. Synthesis of β-*C*-glycoside **2**. Reagents and conditions: (a) (i) AllylMgBr (3.0 equiv), Et_2O, −78 °C, 2 h, 91%, (ii) TFA (6.0 equiv), Et_3SiH (6.0 equiv), CH_2Cl_2, −78 °C, 4 h, 59%. (b) O_3, sudan III indicator, −78 °C, CH_2Cl_2, 15 min, 95%. (c) $NaBH_4$ (5.0 equiv), MeOH, 0 °C, 4 h, 71%. (d) DMP (10.0 equiv), PPTS (0.2 equiv), CH_2Cl_2, rt, 12 h, 83%. DMP = 2,2-dimethoxypropane; PPTS = pyridinium *p*-toluenesulfonate.

Acknowledgments

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15. *Data for β-hydroxy aldehyde* **4**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.36 (m, 5H), 5.77 (dd, $J = 10.9$, 6.8, 1H), 5.39 (d, $J = 11.6$, 1H), 5.21 (d, $J = 17.5$, 1H), 4.55 (s, 2H), 4.26 (dd, $J = 4.5$, 3.9, 1H), 3.75 (m, 2H), 3.33 (br s, 1H), 1.73 (m, 2H), 1.26 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 137.8, 136, 128.5, 127.8, 127.7, 118.4, 73.4, 69.2, 57.8, 30.8, 12.2. IR (neat): 3480, 2865, 1728, 1454, 1367, 1250, 1093, 931, 742 cm^{-1}. R_f at 10% EtOAc in hexanes: 0.32. $[\alpha]_D^{25}$ −38.31 (*c* 0.014, $CHCl_3$). HRMS (EI) Calcd for $C_{15}H_{20}O_3$ (M^+): 248.1412, found: 248.1410.
16. *Data for lactone* **3**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.85 (dd, $J = 11.1$, 6.6, 1H), 5.32 (dd, $J = 17.9$, 11.6, 1H), 4.95 (dd, $J = 8.9$, 1.6, 1H), 4.52 (d, $J = 6.1$, 1H), 3.7 (m, 3H), 2.88 (dd, $J = 13.9$, 4.8, 1H), 2.66 (dd, $J = 16.4$, 2.3, 1H), 1.85 (m, 1H), 1.74 (m, 1H), 1 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 138.1, 128.4, 127.7, 127.6, 117.1, 73.2, 71.6, 66.6, 42.3, 35.8, 30.6, 15.1. IR (neat): 3445, 3014, 2977, 2934, 2870, 1724, 1380, 1237, 1213, 1102, 1074, 758 cm^{-1}. R_f at 60% EtOAc in hexanes: 0.35. $[\alpha]_D^{25}$ −58.23 (*c* 0.005, $CHCl_3$). HRMS (EI) Calcd for $C_{17}H_{22}O_4$ (M^+): 290.1518, found: 290.1510.
17. We have utilized the Molander–Reformatsky intramolecular aldol reaction during the synthesis of both diospongins A and B and the partial synthesis of (−)-lasonolide A. Our observed modest to good yields of 51–55% (Refs. 7d and 9k) are consistent with the reported values by Molander as described in Ref. 11.
18. *Data for β-C-glycoside* **2**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.82 (m, 2H), 5.26 (d, $J = 11.0$, 1H), 5.17 (d, $J = 18.0$, 1H), 5.04 (dd, $J = 17.0$, 8.8, 2H), 4.5 (dd, $J = 20.5$, 12.0, 2H), 3.96 (d, $J = 9.5$, 1H), 3.79 (m, 1H), 3.6 (m, 3H), 2.27 (m, 1H), 2.15 (m, 1H), 1.73 (m, 1H), 1.65 (m, 2H), 1.03 (s, 3H), 0.98 (t, $J = 7.6$, 9H), 0.61 (q, $J = 7.6$, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 135.3, 128.6, 127.8, 127.7, 116.6, 116.5, 108.8, 73.6, 73.6, 73.2, 71.5, 68, 43.7, 40.6, 34.4, 31, 16.8. IR ($CDCl_3$): 3422, 2935, 2887, 2372, 1727, 1419, 1069 cm^{-1}. R_f at 20% EtOAc in hexanes: 0.35. $[\alpha]_D^{25}$ −6.2 (*c* 0.04, $CHCl_3$). HRMS (EI) Calcd for $C_{20}H_{28}O_3$ (M^+): 316.2038, found: 316.2038.