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# Lasonolide A: Structural Revision and Synthesis of the Unnatural (−)-Enantiomer

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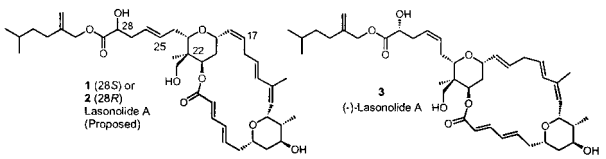
Lasonolide A (proposed structure: **1** or **2**) is a novel macrolide isolated from the shallow water Caribbean marine sponge, *Forcepia* sp.[1] It is a potent cytotoxin against the A-549 human lung carcinoma and P388 murine leukemia cell lines, and inhibits cell adhesion in the EL-4.IL-2 cell line. We synthesized compounds **1** and **2**,[2] and



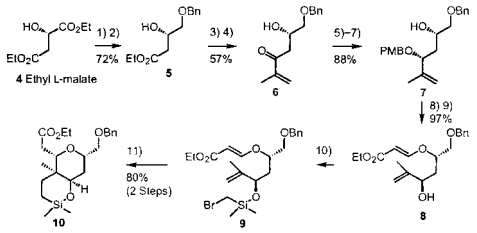

found that neither corresponded with the structure of the natural product. Herein we wish to report a synthesis[3] of the compound **3**, the unnatural enantiomer of lasonolide A.

Preparation of the first tetrahydropyran fragment started with ethyl L-malate (**4**), which was converted into the enone **6** via the Weinreb amide derivative of the ester **5**. Stereoselective reduction[4] of **6** provided the syn diol, and regioselective reduction of the cyclic PMB acetal yielded the triol derivative **7**. The $\beta$-alkoxyacrylate **8** was obtained from **7** via reaction with ethyl propiolate and PMB-deprotection. Radical cyclization reaction[5] of the bromomethyl-(dimethyl)silyl derivative **9** proceeded smoothly and the bicyclic product **10** was obtained as a single product[6] (Scheme 1).

Reduction of the ester group and reaction with pivaloyl chloride provided the pivaloate derivative of **10**, which was converted into the diol **11** via Tamao oxidation.[7] Selective deprotection of the bis-(TBS) derivative of **11** yielded the primary alcohol **12**. Conversion of **12** into the lower homologue **13** required selenide substitution/selenoxide elimination, osmium tetroxide dihydroxylation/sodium periodate cleavage, and sodium borohydride reduction. The aldehyde **14** was synthesized via TBS deprotection of **13**, acetonide protection, benzyl ether deprotection, and oxidation with sulfur trioxide−pyridine complex. The aldehyde **14** was converted to the *trans* olefin **16** via Kocienski−Julia reaction[8] with the sulfone **15**. The sulfone **18** was then obtained after TBDPS deprotection, Mitsunobu-type substitution with 2-mercaptobenzothiazole (**17**), and selective oxidation[9] (Scheme 2).

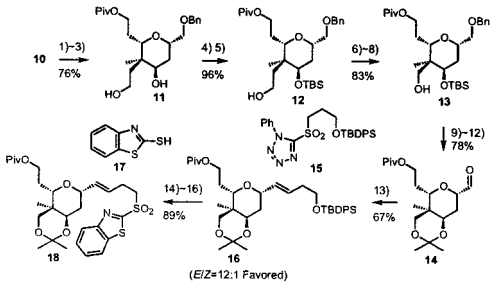
The Evans chiral imide **19** served as the starting material for the synthesis of the second tetrahydropyran fragment. The aldol product from the reaction of the (*Z*)-boron enolate of **19** and benzyloxyacetaldehyde was converted into the hydroxy enone **20** via vinyl Grignard reaction of the corresponding Weinreb amide.[10] After stereoselective reduction of **20**, the product syn diol was converted into the dibenzyl ether **21** via regioselective reduction of the corresponding benzylidene acetal. Osmium tetroxide dihydroxylation/sodium periodate cleavage followed by sodium borohydride reduction provided a primary alcohol, from which the TBS ether **22** was obtained via selective silylation. Reaction of **22** with ethyl propiolate provided the corresponding $\beta$-alkoxyacrylate, which was converted into the bromide **23** via TBS deprotection and

***Scheme 1***[a]




[a] 1) 1.03 equiv $BH_3$·$SMe_2$, 0.05 equiv $NaBH_4$, THF, rt 1 h; 2) 1.0 equiv $Bu_2SnO$, benzene, reflux (−$H_2O$), 16 h; 2.0 equiv BnBr, 1.0 equiv TBAI, reflux, 4 h; 3) 3.0 equiv MeNH(OMe)·HCl, 3.0 equiv $Me_3Al$, THF, 0 °C to rt 5 h; 4) 3.0 equiv $H_2CC(Me)MgBr$, THF, rt 5 h; 5) 1.1 equiv $Et_3B$, 1.1 equiv $NaBH_4$, THF−MeOH (4:1), −78 °C, 5 h; 6) 2.5 equiv (*p*-MeO)$PhCH(OMe)_2$, 0.05 equiv CSA, DCM, rt 1 h; 7) 2.5 equiv DIBAL, DCM, rt 5 h; 8) 1.5 equiv $HCCCO_2Et$, 0.2 equiv NMM, MeCN, rt 2 d; 9) 1.1 equiv DDQ, DCM−$H_2O$, rt 1 h; 10) 1.2 equiv $BrCH_2SiMe_2Cl$, 1.4 equiv TEA, 0.05 equiv DMAP, benzene, rt 30 min; 11) 1.5 equiv $Bu_3SnH$, 0.2 equiv AIBN, benzene (0.02 M), reflux, 5 h (syringe pump, 4 h).

***Scheme 2***[a]




[a] 1) 1.0 equiv $LiBH_4$, ether, rt 6 h; 2) 1.5 equiv PivCl, 0.05 equiv DMAP, 2.0 equiv pyridine, DCM, rt 8 h; 3) ex. 30% $H_2O_2$, 3.0 equiv KF, 4.0 equiv $KHCO_3$, THF−MeOH (1:1), rt 36 h; 4) 3.0 equiv TBSOTf, 5.0 equiv 2,6-lutidine, DCM, rt 8 h; 5) 0.2 equiv CSA, MeOH, 0 °C, 90 min; 6) 1.3 equiv (*o*-$NO_2$)PhSeCN, 1.3 equiv $Bu_3P$, THF, rt 2 h; ex. 30% $H_2O_2$, rt 5 h; 7) 0.05 equiv $OsO_4$, 3.0 equiv NMO, acetone−$H_2O$ (3:1), rt 2 d; 3.0 equiv $NaIO_4$, rt 5 h; 8) 2.0 equiv $NaBH_4$, EtOH, 0 °C, 10 min; 9) concd HCl, MeOH, rt 5 h; 10) 1.5 equiv $Me_2C(OMe)_2$, 0.05 equiv PPTS, acetone, rt 2 h; 11) $H_2$, Pd/C, MeOH, rt 2 h; 12) 5.0 equiv $SO_3$·pyridine, 10 equiv TEA, DMSO−DCM (1:1), 0 °C, 1 h; 13) 1.8 equiv **15**, 1.8 equiv LHMDS, THF−HMPA (5:1), −78 °C; 1.0 equiv **14**, −78 °C to rt 12 h; 14) 1.5 equiv TBAF, THF, rt 3 h; 15) 1.5 equiv $Ph_3P$, 1.5 equiv DIAD, 1.5 equiv **17**, THF, 0 °C, 1 h; 16) 2.0 equiv $(NH_4)_6Mo_7O_{24}$, 30 equiv $H_2O_2$, EtOH, 0 °C, 2 h.

bromide substitution. Radical cyclization of **23** proceeded uneventfully to give the tetrahydropyranyl intermediate **24** in high yield. Benzyl deprotection via hydrogenolysis and silylation provided the bis(TBS) ether analogue of **24**, which was converted into the corresponding aldehyde via lithium borohydride reduction and oxidation with sulfur trioxide−pyridine complex. The *trans*-iodovinyl derivative **25** was obtained by adopting the Takai protocol.[11] Generation of the primary hydroxy group via selective TBS deprotection and oxidation with sulfur trioxide−pyridine led to the production of the corresponding aldehyde in good yield, from



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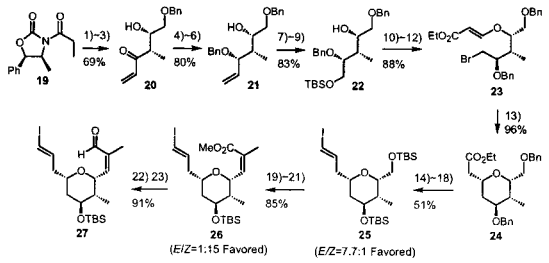
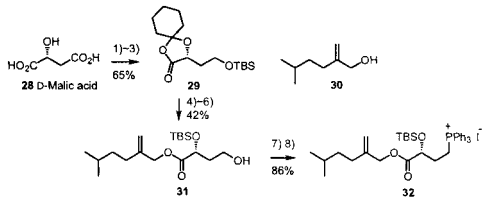
**Scheme 3**[a]



[a] 1) 1.1 equiv *n*-$Bu_2BOTf$, 1.2 equiv TEA, DCM, 0 °C, 30 min; 1.2 equiv $BnOCH_2CHO$, −78 to 0 °C, 2 h; 2) 3.5 equiv MeNH(OMe)·HCl, 3.5 equiv $Me_3Al$, THF, 0 °C to rt 8 h; 3) 3.0 equiv $H_2CCHMgBr$, THF, rt 3 h; 4) 1.2 equiv $Et_3B$, 1.2 equiv $NaBH_4$, THF−MeOH (2.5:1), −78 °C, 5 h; 5) 1.5 equiv, $PhCH(OMe)_2$, 0.05 equiv CSA, DCM, rt 1 h; 6) 2.5 equiv DIBAL, DCM, rt 1 h; 7) 0.05 equiv $OsO_4$, 3.0 equiv NMO, acetone−$H_2O$ (3:1), rt 16 h; 2.0 equiv $NaIO_4$, rt 1 h; 8) 1.5 equiv $NaBH_4$, EtOH, 0 °C, 30 min; 9) 1.1 equiv TBSCl, 1.3 equiv imidazole, DCM, 0 °C, 1 h; 10) 1.5 equiv $HCCCO_2Et$, 0.2 equiv NMM, MeCN, rt 2 d; 11) concd HCl, MeOH, 0 °C, 90 min; 12) 1.5 equiv $CBr_4$, 1.4 equiv $Ph_3P$, 3.0 equiv pyridine, DCM, 0 °C to rt 2 h; 13) 1.5 equiv $Bu_3SnH$, 0.2 equiv AIBN, benzene (0.02 M), reflux, 4 h (syringe pump, 3 h); 14) $H_2$, Pd/C, MeOH, rt 3 h; 15) 3.0 equiv TBSOTf, 5.0 equiv 2,6-lutidine, DCM, rt 3 h; 16) 1.2 equiv $LiBH_4$, ether, rt 12 h; 17) 4.0 equiv $SO_3$·pyridine, 8.0 equiv TEA, DMSO−DCM (1:1), 0 °C, 1 h; 18) 7.5 equiv $CrCl_2$, 2.0 equiv $CHI_3$, dioxane−THF (6:1), rt 10 h; 19) 0.2 equiv CSA, MeOH, rt 1 h; 20) 4.0 equiv $SO_3$·pyridine, 8.0 equiv TEA, DMSO−DCM (1:1), 0 °C, 1 h; 21) 1.5 equiv $MeO_2C(Me)CHPO(OCH_2CF_3)_2$, 1.5 equiv KHMDS, 2.0 equiv 18-c-6, THF, −78 °C, 1 h; 22) 2.5 equiv DIBAL, DCM, −78 °C, 1 h; 23) 20 equiv $MnO_2$, DCM, rt 12 h.

**Scheme 4**[a]



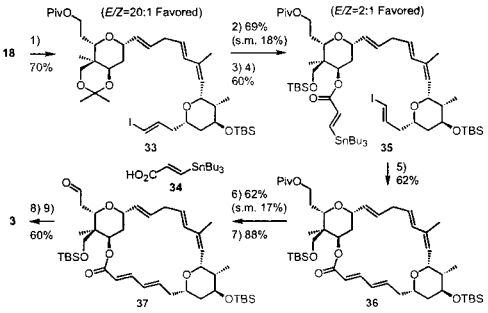
[a] 1) 1.0 equiv cyclohexanone, 1.5 equiv $BF_3$·$OEt_2$, ether, 0 °C to rt 20 h; 2) 3.0 equiv $BH_3$·DMS, 3.0 equiv $B(OMe)_3$, THF, 0 °C to rt 8 h; 3) 1.2 equiv TBSCl, 1.5 equiv imidazole, DCM, rt 1 h; 4) 3.0 equiv **30**, 1.0 equiv NaH, THF, rt 1 h; 5) 1.3 equiv TBSCl, 1.5 equiv imidazole, 0.05 equiv DMAP, DCM, rt 12 h; 6) HF·pyridine, pyridine, THF, rt 1 h; 7) 1.5 equiv $Ph_3P$, 1.5 equiv $I_2$, 3.0 equiv imidazole, THF, rt 1 h; 8) 2.0 equiv $Ph_3P$, MeCN, reflux, 16 h.

which the (*Z*)-enoate **26** was prepared following the Still procedure.[12] The aldehyde **27** was in turn obtained from **26** (Scheme 3).

Synthesis of the side chain fragment started from D-malic acid (**28**), which was converted into the ketal **29** after selective ketal formation, borane reduction, and TBS protection. After reaction of **29** with the alcohol **30**, the primary alcohol **31** was obtained via TBS protection and selective TBS deprotection. The phosphonium salt **32** was prepared from the alcohol **31** via iodide substitution (Scheme 4).

Julia−Julia reaction between the sulfone **18** and the aldehyde **27** generated the *trans* double bond producing the intermediate **33**. Careful acetonide deprotection and selective silylation led to the formation of the corresponding secondary alcohol, and esterification with the acid **34** led to the preparation of the *trans*-$\beta$-stannylacrylate **35**: the undesired *cis*-$\beta$-stannylacrylate isomer was easily separated and recycled under basic conditions. Intramolecular Stille coupling reaction of **35** proceeded uneventfully to provide the macrolactone **36**, which was converted into the aldehyde **37**. Wittig reaction between the ylide prepared from **32** and the aldehyde **37** led to the product **3** after subsequent TBS deprotection (Scheme 5).

**Scheme 5**[a]



[a] 1) 1.2 equiv LDA, THF, −78 °C; 1.3 equiv **27**, THF, −78 °C to rt 10 h; 2) 0.005 M CSA, MeOH, 50 equiv $(HOCH_2)_2$, rt 8 h; 3) 3.0 equiv TBSCl, 5.0 equiv imidazole, DCM, rt 2 h; 4) 3.0 equiv **34**, 4.0 equiv DIC, 2.5 equiv DMAP, DCM, rt 20 h; 5) 0.1 equiv $Pd_2dba_3$, 10 equiv DIPEA, NMP (0.004 M), rt 16 h; 6) 5.0 equiv $LiEt_3BH$, THF, −78 °C, 1 h; 7) 5.0 equiv $SO_3$·pyridine, 10 equiv TEA, DMSO−DCM (1:1), 0 °C, 2 h; 8) 6.0 equiv **32**, 5.5 equiv KHMDS, THF, −78 °C, 1.0 equiv **37**, 5 min; −78 °C to rt 10 h; 9) ex. HF·pyridine, ex. pyridine, THF, rt 16 h.

Comparison of the NMR spectra revealed that **3** represented the correct structure of lasonolide A except the specific rotation, which was opposite to the reported value for the natural product.[13] In the present studies, an excellent stereocontrol was achieved in the introduction of the quaternary center at C-22 via 6-*endo*, 6-*exo* tandem radical cyclization reactions of a $\beta$-alkoxyacrylate.

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**Supporting Information Available:** Selected experimental procedures and spectral data for **1**, **2**, **3**, and other isomers, and further schemes and references (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The reported value[1] for natural lasonolide A: $[\alpha]_D$ +24.4 (*c* 0.045, $CDCl_3$). The value obtained for **3**: $[\alpha]^{20}{}_D$ −24.1 (*c* 0.055, $CDCl_3$). The unnatural enantiomer **3** was obtained in 0.68% total yield from ethyl L-malate (**4**) in 36 steps in the longest sequence.

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