Natural Product Synthesis

Total Synthesis of Natural (+)-Lasonolide A**

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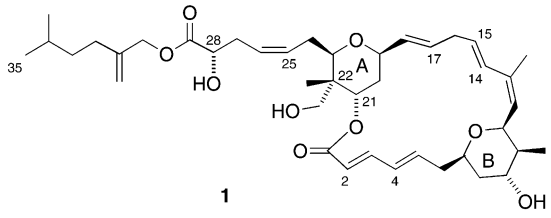
The novel 20-membered macrolide lasonolide A (**1**) was isolated from the Caribbean marine sponge *Forcepia* sp.[1] Lasonolide A displayed antitumor activity by inhibiting the



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in vitro proliferation of A-549 human lung carcinoma cells and interdicting cell adhesion in a cell assay for the detection of signal-transduction agents.[2] The relative stereochemistry of lasonolide A was originally proposed incorrectly based on extensive 2D NMR spectroscopic studies. Its structure was

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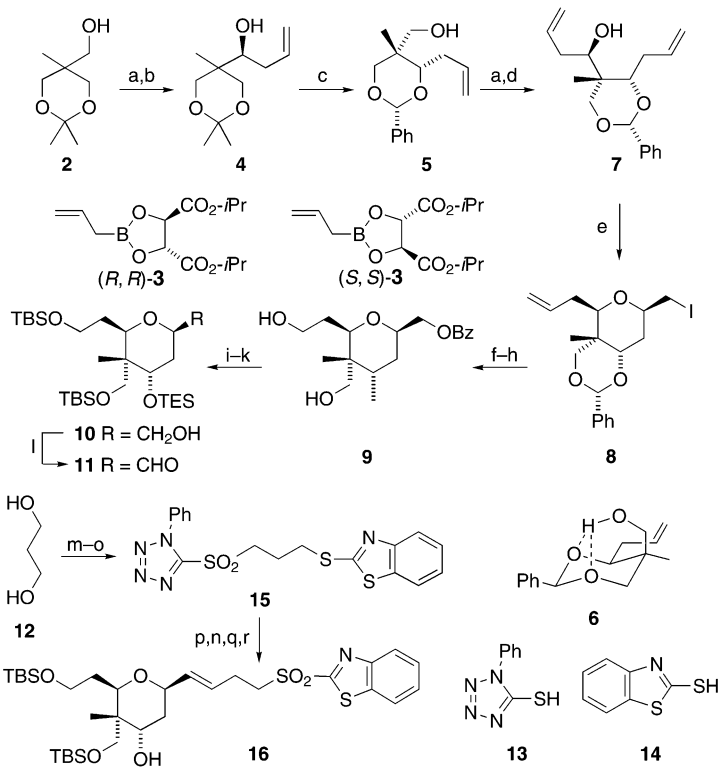
later revised as **1**, with the stereochemistry of the hydroxy-substituted epimerizable C28 center and the absolute configuration shown, based on synthetic studies.[3,4] The intriguing structural features and significant biological activity of this natural product led us to undertake its total synthesis. Herein, we describe a highly enantioselective total synthesis of the natural (+)-lasonolide A (**1**).

Retrosynthetically, we envisaged that double bonds could be introduced at C25 by a Wittig olefination of **27**, at C2 by an intramolecular Horner–Emmons reaction of the α,β-unsaturated aldehyde derived from **25**, and at C14 and C17 by the Julia–Kocieński sulfone-coupling protocol[5] (Scheme 3). Formation of the two *cis*-2,6-disubstituted tetrahydropyran rings by iodoetherification of **7** in the case of the A ring (Scheme 1) and by the intramolecular Michael addition of **19** in the case of the B ring (Scheme 2) was planned, and the choice of protecting groups turned out to be crucial for high stereoselectivity to be observed in these transformations. It was planned to install the C22 quaternary chiral center through the thermodynamic equilibration of **4**.

To secure subunit **16** with the tetrahydropyran ring A, the known alcohol **2**[6] was oxidized and then allylated with the allylboronate (*R*,*R*)-**3** of Roush et al.[7] to give the homoallylic alcohol **4** with 78% *ee* (Scheme 1). The next step was contrived to differentiate the two methylene groups of the 1,3-dioxane ring diastereoselectively and put in place the C22 quaternary stereogenic center. Based on the presumed increased thermodynamic stability caused by hydrogen bonding between the axial hydroxymethyl group and the two oxygen atoms of the acetal as suggested in **6**, the tandem conversion of **4** into the benzylidene **5** was explored extensively under a variety of acidic conditions. A remarkable result was observed when **4** was treated with benzaldehyde in the presence of trifluoroacetic acid (4 equiv). This reaction furnished a 5:1 separable mixture of the desired benzylidene **5** and the diastereomeric acetal with the hydroxymethyl group in an equatorial position, in 72% combined yield. Two other diastereomers in which the benzylidene acetal was formed with the two primary hydroxy groups were produced in 24% combined yield. After one recycling step with the undesired diastereomeric benzylidenes, compound **5** was produced in a total yield of 82%. Swern oxidation[8] of **5**, followed by a second asymmetric allylation, this time with (*S*,*S*)-**3**, gave the alcohol **7** with an enhanced *ee* value of 91%. It was found that the cyclic acetal protecting group was beneficial for the stereoselective formation of ring A. Compound **7** underwent cyclization in the presence of iodine to afford a 27:1 mixture of the *cis*-2,6-disubstituted tetrahydropyran **8** and the corresponding *trans* isomer. The iodide **8** was subjected to a reaction sequence involving substitution, ozonolysis, a reductive workup, and removal of the benzylidene group by hydrogenolysis. The primary and secondary hydroxy groups of the resulting triol **9** were differentially silylated with TBSCl and TESOTf, respectively, and the benzoate group was then hydrolyzed to provide the alcohol **10**.



Scheme 1. a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78→0 °C; b) (*R*,*R*)-**3**, 4-Å MS, PhMe, −78 °C→RT; 2 N NaOH, 0 °C, 86% (for steps a and b); c) PhCHO (3 equiv), CF_3CO_2H (4 equiv), PhMe, −20→0 °C, 82% (after one recycling step); d) (*S*,*S*)-**3**, 4-Å MS, PhMe, −78 °C→RT; 2 N NaOH, 0 °C, 77% (for steps a and d); e) I_2, K_2CO_3, MeCN, −30→−20 °C, 95%; f) BzONa, NMP, 100 °C, 97%; g) O_3, $NaHCO_3$, MeOH, −78 °C; $NaBH_4$, 0 °C, 96%; h) H_2, 10% Pd/C, HOAc, MeOH, room temperature, 89%; i) TBSCl, imidazole, DMF, 0 °C, 95%; j) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 98%; k) K_2CO_3, MeOH, room temperature, 91%; l) Dess–Martin periodinane, pyridine, CH_2Cl_2, room temperature; m) **13**, DEAD, Ph_3P, THF, 0 °C, 81%; n) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, H_2O_2, phosphate buffer (pH 7.6), THF, EtOH, room temperature; o) **14**, DEAD, Ph_3P, THF, 0 °C, 75% (for steps n and o); p) KHMDS, DME, −70 °C→RT, 95% (for steps l and p); q) *p*-TsOH·H_2O, MeOH, room temperature; r) TBSCl, imidazole, DMF, room temperature, 88% (for steps n, q, and r). DMSO = dimethyl sulfoxide, MS = molecular sieves, Bz = benzoyl, NMP = 1-methyl-2-pyrrolidinone, TBS = *tert*-butyldimethylsilyl, DMF = *N*,*N*-dimethylformamide, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, DEAD = diethyl azodicarboxylate, HMDS = bis(trimethylsilyl)amide, DME = 1,2-dimethoxyethane, Ts = toluenesulfonyl.

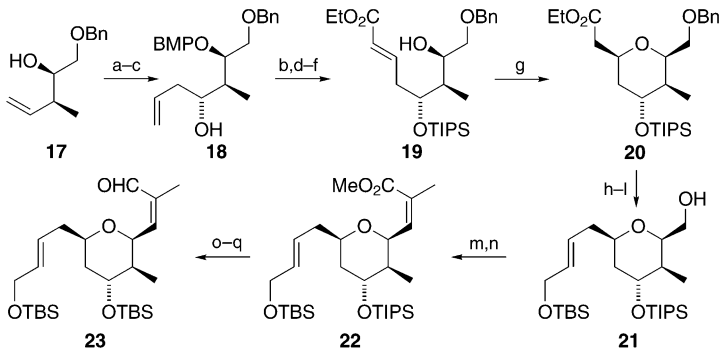
We chose the disulfone equivalent **15** as a suitably functionalized substrate for the introduction of the three carbon atoms required in the target fragment in addition to those present in the alcohol **10** and the later introduction of the *trans* double bonds at C14 and C17. The diol **12** was treated with the tetrazolethiol **13** under Mitsunobu conditions, and the product was oxidized to the corresponding sulfone and then converted into the sulfone–sulfide **15** through a second Mitsunobu reaction with the thiazolethiol **14**. The coupling of the aldehyde **11**, derived from **10**, with **15** was carried out in the presence of KHMDS to give the expected diastereomeric alkenes (*trans*/*cis* 31:1), which were

separated by chromatography. The synthesis of the subunit **16** was completed by oxidation and protecting-group manipulation of the *trans* olefinic sulfide. Whereas the heptamolybdate oxidation of the sulfide to the sulfone under normal conditions[9] proceeded very slowly with partial desilylation, the reaction in the presence of a phosphate buffer was efficient and reached completion within a few hours.

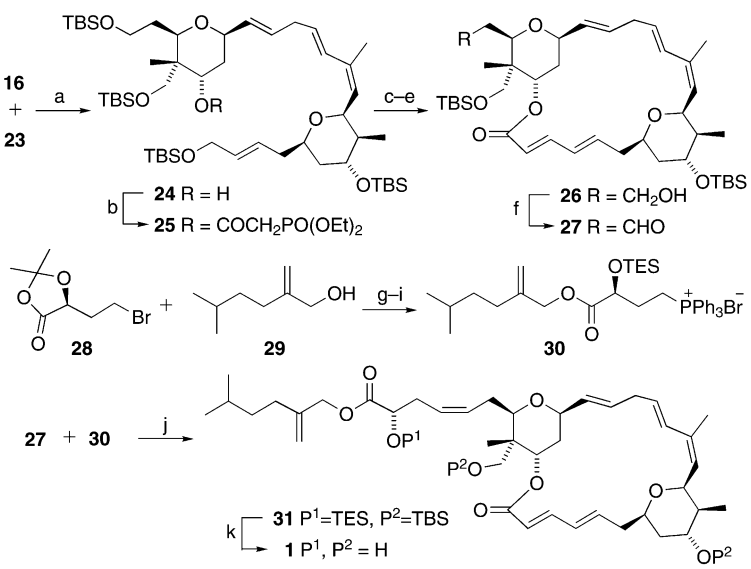
The synthesis of subunit **23**, which contains tetrahydropyran B, started with the *p*-methoxybenzylation of the known alcohol **17**,[10] followed by oxidative cleavage and asymmetric allylation according to the method of Brown et al.[11] to yield the homoallylic alcohol **18**, no diastereoisomers of which could be isolated in appreciable amounts (Scheme 2). After oxidative cleavage of the double bond and conversion of the resulting aldehyde into conjugated ethyl esters (*trans*/*cis* 24:1), the *trans* isomer was subjected to silylation of the alcohol functionality and oxidative removal of the PMB protecting group to furnish the hydroxyester **19**. The intramolecular Michael addition of **19** produced the *cis*-2,6-disubstituted tetrahydropyran **20** as a single stereoisomer. Compound **20** was reduced to the corresponding aldehyde and then treated under olefination conditions to give the expected conjugated esters (*trans*/*cis* 22:1). The *trans* isomer was then sequentially reduced, debenzylated, and monosilylated to afford the alcohol **21**. Swern oxidation of **21** followed by olefination with the trifluoroethyl phosphonate of Still and Gennari[12] provided the conjugated ester **22** (*cis*/*trans* 6.6:1). As all attempts at the desilylation of TIPS-protected lasonolide A proved abortive in the last stage of our synthesis, the TIPS group of the *cis* conjugated ester **22** was exchanged for a TBS group, and the resulting ester was reduced to the aldehyde to yield the tetrahydropyran subunit **23**.

A mixture of the C3–C14 and C15–C25 subunits **16** and **23** was treated with LiHMDS to give a mixture of the coupling product **24** and its *cis* isomer at the newly formed double bond in a $>20{:}1$ ratio (Scheme 3). As the *trans*,*trans*-2,4-dienyl carboxylic acid prepared from **24** and substituted with a hydroxy group at C21 was resistant to macrolactonization in our hands, compound **24** was converted into the phosphonoacetate **25** so that a Horner–Emmons olefination could be employed for the macrocyclization. After removal of the two sterically less hindered TBS groups of **25**, the resulting diol was subjected to allylic oxidation and cyclization mediated by K_2CO_3 in the presence of [18]crown-6[13] to furnish the macrolactone **26** smoothly. Compound **26** was then oxidized to the aldehyde **27**. The C26–C35 side chain required for the construction of the complete lasonolide A skeleton was obtained as the phosphonium salt **30** from the known acetonide **28**[14] and alcohol **29**[15] by acid-mediated esterification, followed by silylation and nucleophilic substitution with PPh_3. The Wittig olefination of **27** and **30** was most effective in the presence of KHMDS, and the protected lasonolide A **31** was desilylated uneventfully to produce the natural (+)-lasonolide A (**1**), all physical and spectroscopic data of which were identical to those reported in the literature.[1,3]

In summary, we have reported a highly enantioselective total synthesis of natural (+)-lasonolide A. The synthesis is characterized by a diastereoselective differentiation step to create the C22 quaternary asymmetric center, the development of the sulfone–sulfide **15** as a three-carbon fragment with two latent *trans* double bonds, cyclizations to form the two *cis*-2,6-disubstituted tetrahydropyrans, and an intramolecular Horner–Emmons reaction to effect macrocyclization.



Scheme 2. a) NaH, PMBCl, nBu$_4$NI, DMF, THF, room temperature, 97%; b) OsO_4, $NaIO_4$, H_2O, THF, room temperature; c) (−)-Ipc$_2$BCH$_2$CH=CH$_2$, Et_2O, −78 °C; 3 N NaOH, H_2O_2, room temperature, 74% (for steps b and c); d) Ph_3P=CHCOOEt, PhH, reflux, 87% (for steps b and d); e) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 98%; f) DDQ, H_2O, CH_2Cl_2, room temperature, 87%; g) NaH, THF, −78→−20 °C, 81%; h) DIBAL, CH_2Cl_2, −78 °C; i) $EtO_2CCH_2PO(OEt)_2$, NaH, THF, −78 °C, 89% (for steps h and i); j) DIBAL, CH_2Cl_2, −78 °C, 91%; k) Li, NH_3 (*liq*), THF, −78 °C, 87%; l) NaH, TBSCl, THF, 0 °C, 94%; m) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78→0 °C; n) $MeO_2CCH(Me)PO(OCH_2CF_3)_2$, KHMDS, [18]crown-6, THF, −78 °C, 79% (for steps m and n); o) TBAF, THF, room temperature; p) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; q) DIBAL, CH_2Cl_2, −78 °C, 88% (for steps o–q). PMB = *p*-methoxybenzyl, Ipc = isopinocamphenyl, TIPS = triisopropylsilyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBAL = diisobutylaluminum hydride, TBAF = tetrabutylammonium fluoride.



Scheme 3. a) LiHMDS, DME, −70 °C→RT, 82%; b) $HO_2CCH_2PO(OEt)_2$, DCC, DMAP, CH_2Cl_2, room temperature, 94%; c) PPTS, MeOH, room temperature, 91%; d) MnO_2, EtOAc, room temperature; e) K_2CO_3, [18]crown-6, PhMe, 70→80 °C, 71% (for steps d and e); f) Dess–Martin periodinane, pyridine, CH_2Cl_2, room temperature; g) *p*-TsOH·H_2O, PhMe, room temperature, 85%; h) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; i) Ph_3P, MeCN, reflux, 88% (for steps h and i); j) KHMDS, THF, −60 °C, 86% (for steps f and j); k) HF·py, pyridine, THF, room temperature, 87%. DCC = 1,3-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, PPTS = pyridinium *p*-toluenesulfonate, py = pyridine.

The longest linear synthetic sequence exploited the ready availability of the alcohol **17** in 26 steps and 7.4% overall yield.

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Keywords: allylation · macrolides · natural products · olefination · total synthesis

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