Lasonolide A: Synthesis of A and B Rings via a Cycloetherification Strategy

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This article is dedicated to the memory of Professor Ray Lemieux whose presence at The Ohio State University at an early stage of his career is still remembered.

Abstract: Syntheses of tetrahydropyrans *ent*-**2** and *ent*-**3**, substructures of the A and B rings of the enantiomer of lasonolide A (**1**), are described. The syntheses of *ent*-**2** and *ent*-**3** feature highly stereoselective cycloetherification reactions of *bis*-homoallylic alcohols **7** and **8**.

Key words: tetrahydropyran, cycloetherification, phenylselenenyl chloride, lasonolide A, macrolide

The structure of lasonolide A, a marine natural product isolated from the Caribbean sponge *Forcepia sp.*, was initially assigned on the basis of NMR spectroscopy.[1] Some stereochemical ambiguities in the original assignment were clarified by the Lee group through an elegant series of studies that culminated in a total synthesis of the natural product. These studies established the actual structure of lasonolide A as **1** (Figure 1).[2] Lasonolide A has been the focal point of a number of synthetic studies, most likely due to its potent activity against several tumor cell lines.[3,4] We became interested in lasonolide A for this reason and because of our interest in developing a cycloetherification approach to tetrahydropyrans, a substructure that appears in the A and B rings of **1** and many other natural products.[5] This paper describes syntheses of tetrahydropyrans *ent*-**2** and *ent*-**3**, enantiomers of intermediates in the Lee group synthesis of **1**.

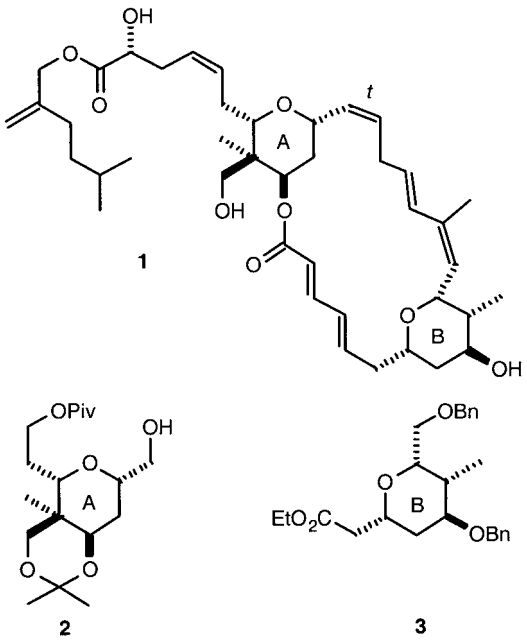
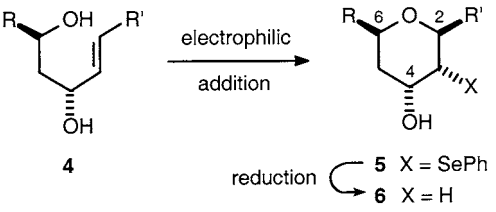


Figure 1

An overview of the cycloetherification approach we have developed for the synthesis of *ent*-**2** and *ent*-**3** is illustrated in Equation 1. We have previously shown that treatment of *bis*-homoallylic alcohols of type **4** with appropriate electrophiles affords tetrahydropyrans of type **5** when R is an appropriate carbocation stabilizing group.[6] Reduction of the electrophile (X → H) then provides a tetrahydropyran of type **6**. Of course there are stereochemical issues associated with this approach. We have addressed some of these issues in earlier work and this paper further delineates what can be expected from complex substitution patterns along the *bis*-homoallylic alcohol backbone.



Equation 1

Application of this approach to the synthesis of *ent*-**2** required the preparation and cyclization of *bis*-homoallylic alcohol **7**. This was accomplished as shown in Scheme 1. Oxidation of commercially available diacetone glucose with PDC-acetic anhydride provided ketone **9** in 89% yield.[7] Conversion of **9** to nitroalkene **10** was then accomplished in 85% overall yield by a modification of literature procedures.[8] Treatment of **10** with lithium dimethylcuprate gave **11** (50–80% yield), and oxidation of the derived nitronate using ozone gave carboxylic acid **12** (85%).[9,10] Acid **12** was reduced with lithium aluminum hydride, and the resulting alcohol **13** was protected as the corresponding benzyl ether **14** (85% from **12**).[11] Hydrolysis of the exocyclic acetonide followed by treatment of the resulting vicinal diol with triphenylphosphine-iodine gave olefin **15** in 65% yield.[12] Hydroboration-oxidation of the olefin followed by etherification of the resulting alcohol **16** gave **17** in 77% yield. The remaining acetonide was hydrolyzed, and Wittig olefination of the resulting hemi-

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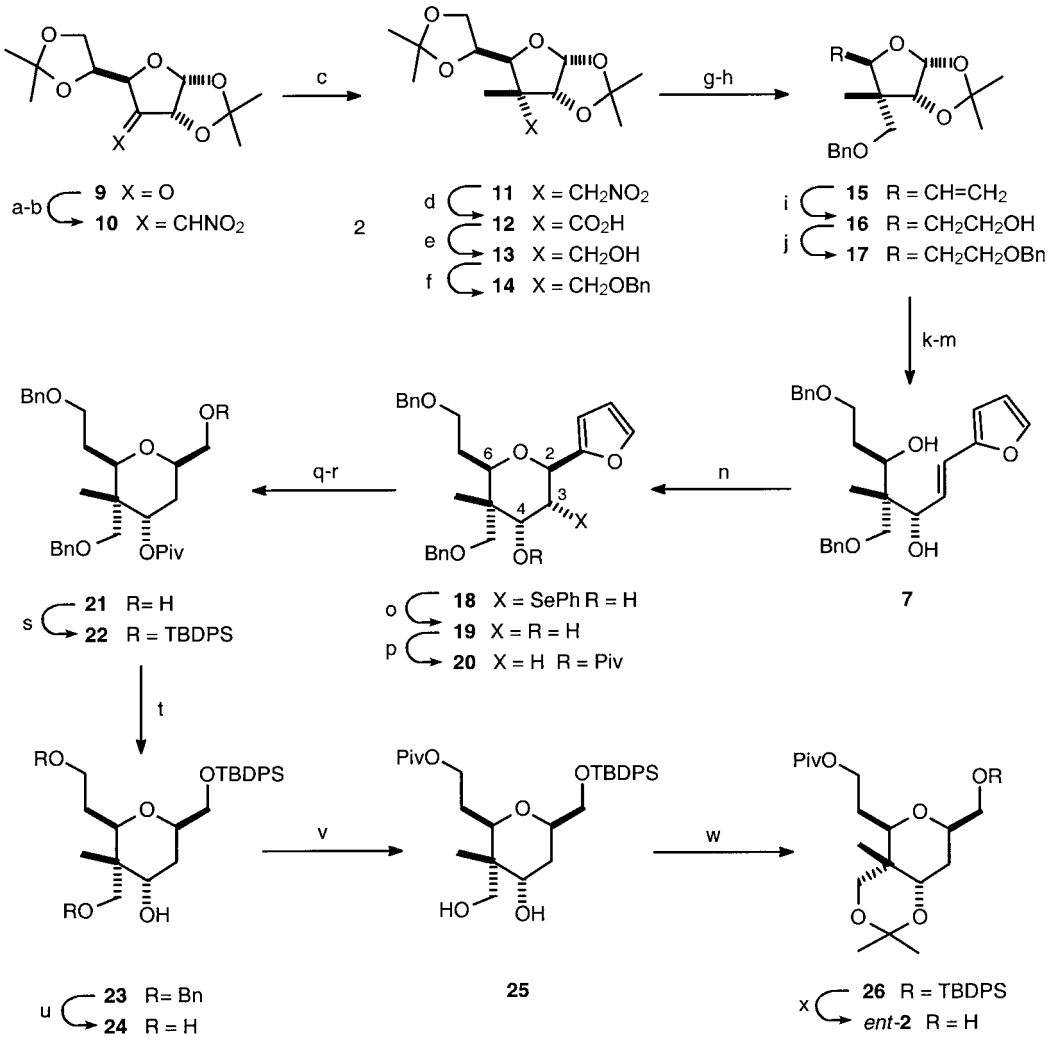
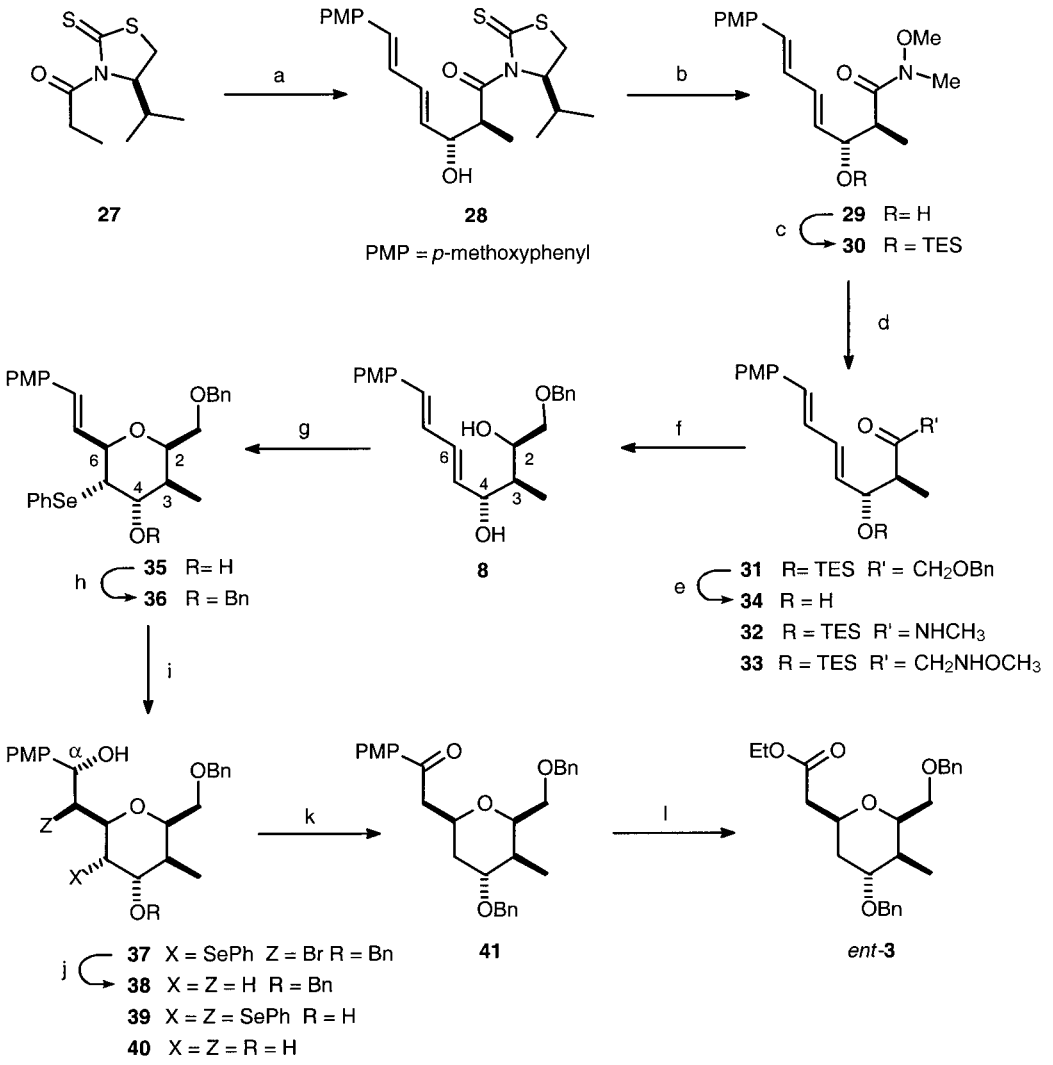


Scheme 1 Synthesis and cyclization of **7**. Reagents: (a) CH_3NO_2, 0.2 N aq NaOH, Bu_4NI, benzene (95%) (b) Ac_2O, DMSO (90%) (c) Me_2CuLi, Et_2O (50–80%) (d) 0.5 M aq NaH_2PO_4–1.0 M aq NaOH (1:1); aq oxone; 10% aq HCl (85%) (e) $LiAlH_4$, THF (95%) (f) $Cl_3CC(=NH)OBn$, CH_2Cl_2–cyclohexane, CF_3SO_3H (90%) (g) 60% aq acetic acid, Δ (81%) (h) Ph_3P, I_2, imidazole, toluene, 80 °C (80%) (I) 9-BBN; 2.0 N aq NaOH–30% aq H_2O_2 (89%) (j) BnBr, Bu_4NI, NaOH (86%) (k) acidic Dowex-50, 50% aq dioxane, 80 °C (70%) (l) Ph_3PCH_2(2-furyl)Br, dioxane, KO-*t*-Bu (86%, *trans:cis* = 3:1) (m) neat *n*-Bu_3SnH, AIBN, 80 °C (99%, *trans:cis* = 30:1) (n) PhSeCl, CH_2Cl_2 (87%) (o) *n*-Bu_3SnH, AIBN, benzene, reflux (88%) (p) *t*-BuCOCl, pyridine (93%) (q) O_3, MeOH (r) BH_3–THF, –10 °C (64% for 2 steps) (s) *t*-$BuPh_2SiCl$, DMF, imidazole (87%) (t) *i*-Bu_2AlH, toluene (72%) (u) H_2, 10% Pd on C (60%) (v) *t*-BuCOCl, pyridine (74%) (w) $Me_2C(OMe)_2$, PPTS (96%) (x) *n*-Bu_4NF, THF (87%)

acetal using (2-furyl)methylidenetriphenylphosphorane[13] gave *E*-olefin **7** and the isomeric *Z*-olefin in a 3:1 ratio, respectively. Isomerization of the mixture of olefins using tri-*n*-butyltin radicals gave **7** (60% from hemiacetal **17**) contaminated with only 3% of its geometrical isomer.[14]

Treatment of **7** with phenylselenenyl chloride gave tetrahydropyran **18** as a single diastereomer in 87% yield.[15] We imagine that the observed stereoselectivity is a result of intramolecular *anti* addition of the electrophile and incipient tetrahydropyran oxygen to the olefin via a chair like conformation that places the C_2 and C_6 substituents in equatorial sites. We have previously shown that C_4 oxygen substituents (TBS ethers and hydroxyl groups) exhibit a preference for axial sites in related cycloetherifications. This effect is consistent with the stereoselectivity observed in the cyclization of **7**.[6]

There are a number of ways in which **18** might be used in a synthesis of *ent*-lasonolide A or derivatives thereof. For characterization purposes, however, we focused on the conversion of **18** to tetrahydropyran *ent*-**2**, the enantiomer of the Lee group intermediate in their synthesis of **1**.[2] This transformation was accomplished as shown in Scheme 1. Reduction of selenide **18** with tri-*n*-butyltin hydride provided **19** in 88% yield.[16] Protection of the secondary hydroxyl group gave pivalate **20** in 93% yield. Oxidative degradation of the furan using ozone followed by reduction of the intermediate crude carboxylic acid with borane–THF gave primary alcohol **21** in 64% yield.[17] Conversion of the primary alcohol to *tert*-butyldiphenylsilyl ether **22** followed by reduction of the pivalate using diisobutylaluminum hydride gave alcohol **23** in 63% yield.[18] Hydrogenolysis of the benzyl groups followed by



Scheme 2 Synthesis and cyclization of **8**. Reagents: (a) $Sn(OTf)_2$, *N*-ethylpiperidine, CH_2Cl_2, –70 °C; (*E*,*E*)-PMPCH=CHCH=CHCHO (79%) (b) CH_2Cl_2, –10 °C, $Me_2AlN(OMe)Me$ (93%) (c) Et_3SiCl, imidazole, DMF (94%) (d) *n*-$Bu_3SnCH_2OCH_2Ph$ (5 equiv), *n*-BuLi (3 equiv) (55–65%) (e) CF_3CO_2H, THF–H_2O (5:1) (f) $Zn(BH_4)_2$, toluene, Et_2O, –78 °C (45–55% for 2 steps) (g) PhSeCl, CH_2Cl_2, –78 °C (55–65%) (h) $PhCH_2Br$, 10 mol% *n*-Bu_4NI, 50% w/w aq NaOH, 60 °C, sonication (64%) (i) NBS, acetone–H_2O (2:1), 0 °C → r.t. (86%) (j) *n*-Bu_3SnH (5 equiv), Et_3B, O_2, PhH, r.t. (95%) (k) Dess–Martin periodinane, CH_2Cl_2, r.t. (l) MCPBA, *p*-TsOH (cat); EtOH, H_2SO_4 (cat), Δ (65%)

esterification of the resulting triol **24** gave diol **25** in 44% yield. The diol was protected as acetonide **26** (96% yield) and the silyl ether was removed using tetra-*n*-butylammonium fluoride to give the target tetrahydropyran *ent*-**2** in 87% yield. Tetrahydropyran *ent*-**2** was identical (^1H and ^{13}C NMR) to material prepared by the Lee group.[19]

Application of this cycloetherification approach to the synthesis of *ent*-**3** required the preparation and cyclization of *bis*-homoallylic alcohol **8**. This was accomplished as shown in Scheme 2. Thiazolidinethione **27** was converted to the corresponding Sn(II) enolate and reacted with *E*,*E*-5-(4-methoxyphenyl)penta-2,4-dienal to provide aldol product **28** in 79% yield.[20,21] The diastereomeric ratio in this reaction was 95:5 (based on integration of the ^1H NMR signals due to the C_2 methyl doublets), and the absolute stereochemistry was assigned by analogy with the many examples of this process reported by Nagao and others.[21] Treatment of **28** with the aluminum amide derived from *N*,*O*-dimethylhydroxylamine gave Weinreb amide **29** in 93% yield along with greater than 80% recovery of the chiral auxiliary.[22] Protection of the secondary alcohol as TES-ether **30** was then accomplished in 94% yield.[23] After considerable experimentation it was found that treatment of one equivalent of **30** with benzyloxymethyllithium (prepared from 5 equivalents of *n*-Bu_3SnCH_2OBn and 3 equivalents of *n*-BuLi) gave ketone **31** in 55–65% yields along with approximately 5% each of amide **32** (probably derived from a β-elimination reaction) and α-aminoketone **33**.[24,25] The TES protecting group of **31** was removed using one equivalent of trifluoroacetic acid in aqueous tetrahydrofuran at room temperature. The resulting alcohol **34** was extremely sensitive to both acid and base. β-Elimination and retro-aldol reactions were both encountered during attempts to purify this material. These problems were minimized when crude **34**

was immediately reduced with zinc borohydride in toluene–diethyl ether at –78 °C.[26] This provided a 4:1 mixture of cyclization substrate **8** and its C_2 epimer, contaminated with some trienol derived from β-elimination of **34** followed by reduction. Treatment of this mixture with phenylselenenyl chloride gave tetrahydropyran **35** in 48% overall yield from **31**, along with a 19% yield of **39** (presumably derived from addition of phenylselenenyl chloride to **35** followed by solvolysis of an intermediate benzylic chloride) as a minor product. The structure of **31** was initially established by NMR spectroscopy and ultimately by correlation with known material (vide infra). The structure of **39** was established by X-ray crystallographic analysis of diol **40**, prepared in 89% yield by reduction of **39** with tri-*n*-butyltin hydride.[27] The stereochemical course of the cyclization of **8** to **35** (and the tetrahydropyran portion of **39**) can once again be rationalized by *anti* addition of the electrophile and incipient tetrahydropyran oxygen across the double bond via a chair-like transition state in which the C_2 and C_6 substituents occupy equatorial sites. This cyclization transition state would require that the incipient C_3 methyl and C_4 hydroxyl groups occupy axial sites in the cyclization transition state. We note that although no other tetrahydropyran stereoisomers were detected, the mass balance for the conversion of **31** to **35** and **39** suggests that minor stereoisomers may have been produced.[28]

Once again, although we imagine there may be a number of ways in which **35** might be used in a synthesis of *ent*-lasonolide A, we focused on correlation of this material with compound *ent*-**3**, the enantiomer of the intermediate used by the Lee group in their approach to **1**. Thus, protection of the secondary hydroxyl group as a benzyl ether (**35** → **36** in 64% yield) followed by bromohydrin formation (NBS in aqueous DMSO) gave a mixture of **37** and the C_α-C_β diastereomer in 86% yield.[29] This mixture was reduced with tri-*n*-butyltin hydride to provide a mixture of **38** and its C_α epimer in 95% yield.[30] Oxidation of this mixture with the Dess–Martin periodinane gave ketone **41** in 89% yield.[31] Bayer–Villiger oxidation of **41** using *m*-chloroperoxybenzoic acid, followed by ethanolysis of the resulting aryl ester, gave tetrahydropyran *ent*-**3** in 65% overall yield.[32] Tetrahydropyran *ent*-**3** was spectroscopically identical (^{1}H and ^{13}C NMR) to material prepared by the Lee.[19]

In summary, it has been shown that the cycloetherification strategy outlined in Equation [1] can be used to prepare the enantiomers of both the A-ring and B-ring intermediates (**2** and **3**) in Lee's synthesis of lasonolide A (**1**). The key cycloetherifications proceed with excellent levels of diastereoselectivity and the overall length of the syntheses of *ent*-**2** and *ent*-**3** are similar to the Lee syntheses of the corresponding enantiomers. Nonetheless, the syntheses are longer than desirable and improvements are needed before this chemistry will provide a practical route to lasonolide A (**1**) and derivatives thereof.[33]

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(27) We thank Dr. Judith C. Gallucci for determining the structure of **40** at the OSU Chemistry Department Crystallographic Facility.
(28) During the course of this work we have examined cyclizations of several structures related to **8** (replace C_6 *p*-methoxystyryl group with phenyl, 2-furyl, styryl). In all cases the structure corresponding to **35** was the major product in 60–70% yield. In one case (styryl) a minor diastereomer (5%) was detected in which all substituents were equatorially disposed on the tetrahydropyran ring with the exception of the benzyloxymethyl group (axially disposed).
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(33) Some of the reagents used in Schemes 1 and 2 are toxic (for example PhSeCl). Appropriate care should be used in the handling and disposal of these materials.