Macrolide Synthesis

Formal Synthesis of Leucascandrolide A**

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Extracts from the calcareous sponge *Leucascandra caveolata* were collected from waters along the northeastern coast of New Caledonia by Pietra and co-workers, and yielded the novel marine macrolide leucascandrolide A (**1**).[1] The structure of **1** was elucidated by extensive 2D NMR experiments and analysis of Mosher ester derivatives, which revealed an 18-membered macrolide containing two bridging trisubstituted tetrahydropyran rings and an ester side chain with a *Z*-α,β-unsaturated oxazole. The natural product displayed significant in vitro cytotoxicity against both KB oral epidermoid carcinoma and P388 leukemia cell lines ($IC_{50} = 0.05$ and $0.25\ \mu g\,mL^{-1}$, respectively), as well as antifungal activity against the pathogenic yeast *Candida albicans*. Attempts to isolate additional quantities of the natural product through subsequent harvesting of sponge samples proved unfruitful, which led to the suggestion that **1** may be derived from the

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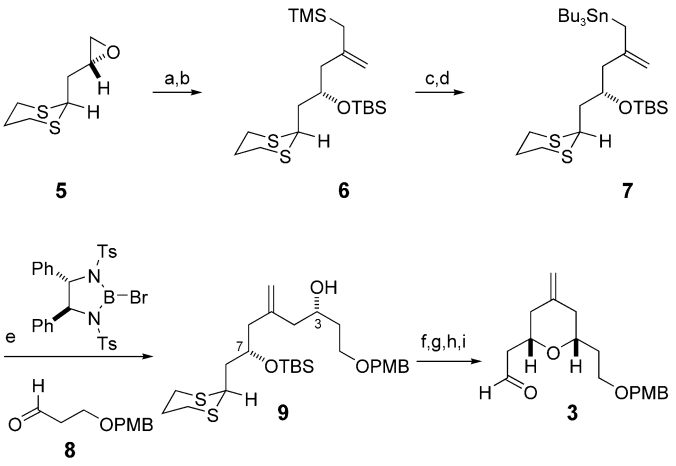
metabolism of microbial species harbored within the sponge.[2] The biological activity and complex molecular architecture of **1** have provided the impetus for several studies toward its synthesis.[3] Recently, total[4] and formal syntheses[5] of leucascandrolide A have been reported by several groups. Herein we describe the culmination of our efforts, which have led to a convergent, highly stereocontrolled formal synthesis of **1** in the preparation of the macrolactone **2**.

Our retrosynthetic analysis of the leucascandrolide A macrolactone **2** inspired an asymmetric allylation strategy based on the nonracemic aldehyde **3** and the complex optically active allyl stannane **4** (Scheme 1). This efficient C9–C10 bond construction would directly incorporate all the carbon atoms necessary for macrocycle formation, and the major stereochemical features associated with the macrolide **2**. Late-stage incorporation of the C18–C23 side chain through an alkenyl zinc addition, and subsequent formation of the allylic alcohol at C17 through an asymmetric hydride reduction would precede the final macrolactonization step.

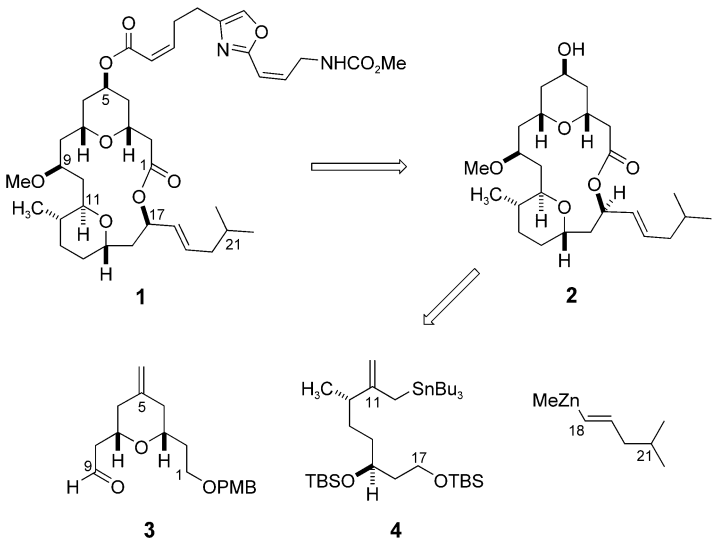
The preparation of the C1–C9 aldehyde **3** commenced with the conversion of the known epoxide **5** (readily available from (+)-epichlorohydrin)[6] into the allyl silane **6** through the copper-catalyzed addition of the Grignard reagent prepared from 2-bromo-3-trimethylsilylpropene (Scheme 2).[7] Subsequent protection of the resulting homoallylic alcohol gave the TBS ether **6**. Treatment of **6** with freshly recrystallized NBS at −78 °C led to the immediate formation of the labile corresponding allylic bromide, which was displaced directly with a tributylstannylcuprate to give the allyl stannane **7**. Asymmetric allylation was effected following the tin-to-boron transmetalation of the allylstannane **7** by using the boron bromide reagent developed by Corey et al., which is derived from a (*S*,*S*)-1,2-diamino-1,2-diphenylethane bis(sulfonamide) and boron tribromide.[8] Nucleophilic addition to the aldehyde **8**[9] provided the *S* homoallylic alcohol **9** as the major component of a mixture of diastereomers epimeric at C3 (100%, d.r. 11:1).[10] Ring closure of **9** to afford the 2,6-*cis*-tetrahydropyranyl moiety of **3** was carried out by conversion of the alcohol at C3 into the corresponding tosylate, removal of the silyl protecting group at C7, and internal backside displacement to yield an 11:1 ratio of diastereomers, which were separated by flash chromatography. Mild hydrolysis of the dithiane was promoted by methylation of the sulfur atoms,[11] which provided the aldehyde **3** in excellent overall yield.



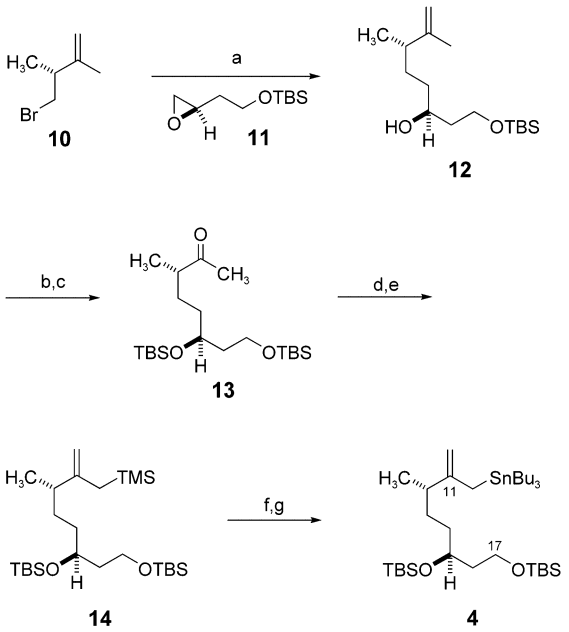
Scheme 2. Reagents and conditions: a) Mg^0, THF, (2-bromoallyl)trimethylsilane; then **5**, CuI, −50 °C; −50→−10 °C, 2 h; 79%; b) TBSCl, imidazole, DMF; 100%; c) NBS, propylene oxide, CH_2Cl_2/DMF (2:3), −78 °C; d) Bu_3SnLi, CuBr·DMS, THF, −78°→−40 °C; 77% (2 steps); e) the (*S*,*S*)-1,2-diamino-1,2-diphenylethane bis(sulfonamide), BBr_3, CH_2Cl_2, 0 °C, 1 h; then **7**, room temperature, 10 h; then **8**, −78 °C, 1.5 h; 100%, d.r. 11:1; f) TsCl, Et_3N, DMAP, CH_2Cl_2; 100%; g) HF·pyr, CH_3CN; 99%; h) NaH, PhH, 90 °C; 75%; i) MeI, $CaCO_3$, CH_3CN/H_2O (9:1), 16 h; 100%. DMAP = 4-(dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, DMS = dimethyl sulfide, NBS = *N*-bromosuccinimide, pyr = pyridine, TBS = *tert*-butyldimethylsilyl, Ts = *p*-toluenesulfonyl.

Preparation of the novel allyl stannane **4** began with the copper(I)-catalyzed addition of the Grignard reagent derived from (2*S*)-1-bromo-2,3-dimethyl-3-butene **10**[12] to the nonracemic epoxide **11**,[13] which led directly to the alcohol **12** in 80% yield (Scheme 3). Protection of the secondary alcohol in **12** as its TBS ether and subsequent oxidative cleavage of the terminal olefin by ozonolysis gave the methyl ketone **13** in excellent yield. Conversion of **13** into the corresponding enol triflate through kinetic deprotonation at low temperature and sulfonate formation by use of the Comins reagent[14] was followed by nickel-catalyzed cross-coupling with (trimethylsilylmethyl)magnesium chloride to provide the allyl silane **14**.[15] As we have noted previously,[10] the transmetalation of allyl silanes to allyl boranes tends to be ineffective. Thus, conversion of **14** into the allyl stannane, as described for **7**, led to the C10–C17 allyl stannane **4** in 77% yield after flash silica-gel chromatography.

Our convergent strategy toward **2** was to examine the selective introduction of asymmetry at C9. This feature was of particular interest for our studies of asymmetric allylation owing to the presence of adjacent asymmetry at C12 in the allyl component **4**, and



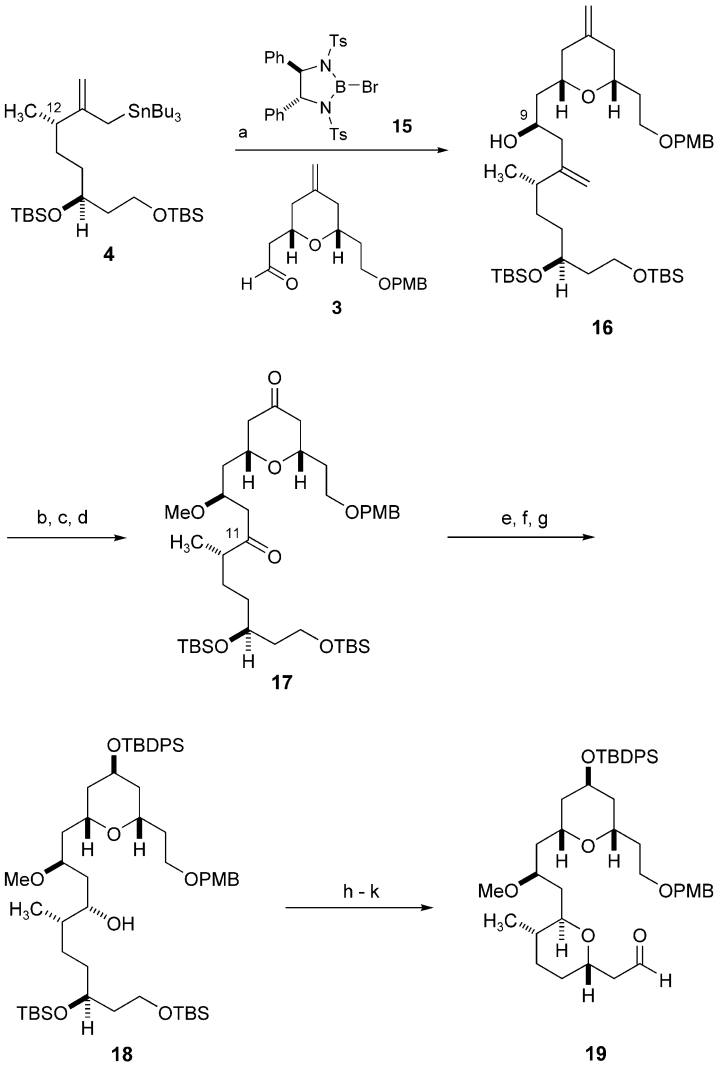
Scheme 1. Retrosynthetic analysis of the leucascandrolide A macrolactone **2**.



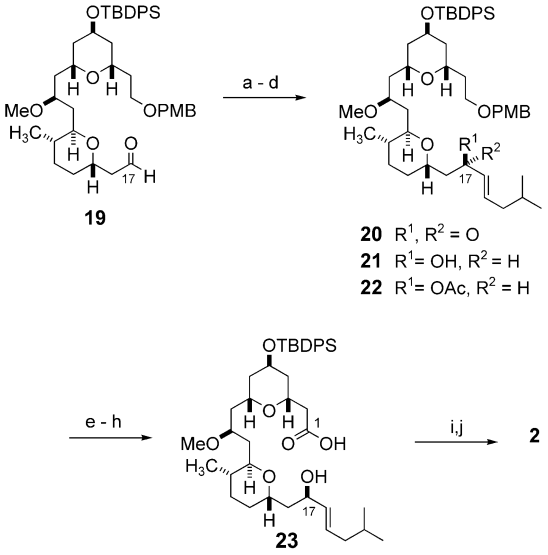
Scheme 3. Reagents and conditions: a) Mg^0, THF, **10**; then CuBr·DMS, THF, −78 °C; then **11**, THF, −78 °C→RT; 80%; b) TBSCl, imidazole, DMF; 96%; c) O_3, CH_2Cl_2/MeOH (1:1), −78 °C; then DMS, −78 °C→RT; 98%; d) KHMDS, THF, −78 °C; then Comins reagent, THF; 87%; e) $[Ni(acac)_2]$, $TMSCH_2MgCl$, THF, room temperature; 75%; f) NBS, propylene oxide, CH_2Cl_2/DMF (3:2), −78→−10 °C; g) Bu_3SnLi, CuBr·DMS, THF, −78°→−40 °C; 77% (2 steps). acac = acetylacetone, Comins reagent = 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, HMDS = hexamethyldisilazide.

the possible formation of diastereotopic transition states in the reaction of the intermediate chiral allyl borane with the aldehyde **3**.[16] The homoallylic alcohol (9*R*)-**16** (95%, d.r. 8.5:1) was prepared by transmetalation of optically pure **4** with the *R*,*R* bromoborane **15** to yield an intermediate allylic borane for low-temperature condensation with the tetrahydropyranyl aldehyde **3** (Scheme 4). Facial selectivity of the nucleophilic addition was dominated by the chiral auxiliary, and the diastereomers were readily separated by flash chromatography. Methylation of the homoallylic alcohol at C9 in **16** was followed by oxidative cleavage (OsO_4, NMO; $NaIO_4$) to provide the corresponding diketone **17**. L-Selectride promoted selective reduction at C5 of the tetrahydropyranone **17**, which led to the corresponding axial alcohol in 84% yield (d.r. > 95:5), and this alcohol was protected as its TBDPS ether. Attention was then focused on the asymmetric reduction of the ketone at C11. The use of the Terashima reagent[17] for selective aluminum hydride reductions of acyclic β,β′-dialkoxy ketones has been reported recently from these laboratories.[18] In this case, the Terashima reduction of the ketone at C11 in the presence of the ligand (−)-*N*-methylephedrine resulted in an effective reagent-based hydride addition with excellent diastereofacial selectivity (d.r. > 95:5) to provide the anti-Felkin product **18** in high yield (95%). To ensure formation of the 2,6-*trans*-tetrahydropyran, tosylation of the alcohol **18** was followed by selective removal of the TBS groups and treatment with sodium hydride. The resulting internal backside displacement led to the exclusive formation of the desired six-membered ring, and Dess–Martin oxidation[19] of the primary alcohol yielded the aldehyde **19**.

To achieve our final objective we required efficient incorporation of the C18–C23 carbon chain and flexibility for the development of stereogenicity at C17.[20] To this end, the hydrozirconation of 4-methyl-1-pentyne with the Schwartz reagent was followed by transmetalation with dimethylzinc as adapted from the reports of Wipf et al.



Scheme 4. Reagents and conditions: a) the (*R*,*R*)-1,2-diamino-1,2-diphenylethane bis(sulfonamide), BBr_3, CH_2Cl_2, 0 °C, 1 h; then **4**, room temperature, 10 h; then **3**, −78 °C, 1.5 h; 96%, d.r. 8.5:1; b) Me_3OBF_4, proton sponge, 4-Å molecular sieves, CH_2Cl_2; 96%; c) OsO_4, NMO, acetone/H_2O (2:1), 16 h; d) $NaIO_4$, THF/phosphate buffer (pH 7; 1:1), 16 h; 80% (2 steps); e) L-Selectride, THF, −78 °C, 1.5 h; 84%; f) TBDPSCl, imidazole, DMF, 40 h; 73%; g) $LiAlH_4$ (2.0 equiv), (−)-*N*-methylephedrine (2.0 equiv), *N*-ethylaniline (4.0 equiv), Et_2O, −78 °C, 2 h; 95%; h) Ts_2O, pyridine, CH_2Cl_2; 100%; i) HF·pyr, pyridine, THF; 84%; j) NaH, PhH, 60 °C, 16 h; 73%; k) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; 95%. NMO = *N*-methylmorpholine *N*-oxide, L-Selectride = lithium tri-*sec*-butylborohydride, TBDPS = *tert*-butyldiphenylsilyl.



Scheme 5. Reagents and conditions: a) 4-methyl-1-pentyne, CH_2Cl_2, $Cp_2Zr(H)Cl$, room temperature; then Me_2Zn, −78 °C; then **19**, −78 °→ 0 °C, 1 h; 87%; b) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; 75%; c) (*S*)-2-methyloxazaborolidine, BH_3·THF, −10 °C; 89%, d.r. 5:1; d) Ac_2O, pyridine, DMAP, CH_2Cl_2; 97%; e) DDQ, CH_2Cl_2/phosphate buffer (pH 7)/*t*BuOH (40:10:1), 1.5 h; quant.; f) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; g) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, aqueous *t*BuOH, 0 °C, 45 min; 56% (2 steps); h) K_2CO_3, MeOH, 16 h; i) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, benzene; 63% (2 steps); j) TBAF, THF; 67%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

(Scheme 5).[21] Reactions of the resulting alkenyl zinc species with the aldehyde **19** resulted in the efficient formation of a mixture of diastereomeric allylic alcohols (1:1 ratio), which was oxidized directly to the enone **20** (75% yield over two steps). Interestingly, the asymmetric hydride reduction of the α,β-unsaturated ketone **20** under Terashima conditions gave rise to conjugate reduction as a major reaction pathway. This result is atypical as the Terashima conditions are generally utilized for the production of chiral allylic alcohols. However, Corey–Bakshi–Shibata (CBS) borohydride reduction[22] of **20** with the CBS reagent (*S*)-2-methyloxazaborolidine in the presence of borane–tetrahydrofuran complex gave an 89% yield of a 5:1 mixture of separable diastereomers, epimeric at C17, in favor of the *R* alcohol **21**. Acetylation to **22** was followed by oxidative deprotection of the alcohol at C1. The seco-acid **23** was obtained by oxidation of the resulting primary alcohol to the carboxylic acid and subsequent basic methanolysis of the acetate at C17. The crude product was subjected to the Yonemitsu-modified Yamaguchi[23] protocol to give the macrolide in good yield (63% over two steps). Finally, deprotection of the alcohol at C5 by treatment with fluoride provided the leucascandrolide A macrolactone **2**, whose physical and spectroscopic data were identical in all respects to those previously reported.[4a] Leighton and coworkers have also described the conversion of **2** into leucascandrolide A, and thus, our efforts constitute a formal synthesis of the natural product **1**.

In summary, our investigations into asymmetric allylation methodology have extended this fundamental technique to the efficient, convergent construction of complex molecules. Our studies have also provided unprecedented results for the use of the Terashima hydride reduction in the stereoselective formation of saturated, acyclic alcohols. Overall, we have carried out an efficient synthesis of the leucascandrolide A macrolactone **2** with a high level of stereoselectivity. Further studies are in progress in our laboratory.

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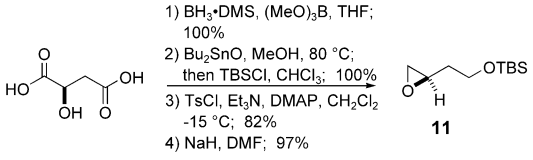

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