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A formal total synthesis of leucascandrolide A

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A convergent synthesis of the macrocyclic core of the marine macrolide leucascandrolide A has been accomplished.

Leucascandrolide A (Fig. 1) is a structurally unique macrolide isolated in 1996 from the sponge *Leucascandra caveolata*.[1] The natural product has been shown to possess impressive anticancer and antifungal activities. This synthetically appealing structure, in combination with its remarkable biological activity, has solicited considerable interest in the synthetic community. Leighton and coworkers[2] published the first total synthesis of leucascandrolide A in 2000, and one formal total synthesis[3] and several fragment preparations[4] have been reported. We now report a synthesis of the macrocyclic core of leucascandrolide A, which constitutes a second formal total synthesis of the natural product.

Our retrosynthetic analysis of the macrocycle simplified the structure into two major fragments, with the key disconnection at the C_9–C_{10} bond. We anticipated that a C_9-dithiane/C_{10}-iodide coupling would effectively unite the two fragments. The synthesis of the C_1–C_9 dithiane began with the known allyl sulfide **1**[5] (Scheme 1). Lithiation of **1** with *n*-BuLi followed by addition of *m*-xylylene dibromide furnished the bis-sulfide **2** in 78% yield. A double Mislow-Evans rearrangement[6] was induced by oxidation to the bis-sulfoxide with *m*-chloroperoxybenzoic acid and subsequent reductive trapping of the sulfenate ester with diethylamine to provide diol **3** in 81% yield with complete *trans*-selectivity. Monoprotection[7] with TBSCl, Sharpless asymmetric epoxidation[8] with (−)-diisopropyl tartrate (86%, 97% ee by Mosher's ester analysis) and reductive opening of the epoxide with Red–Al gave diol **4**. The primary alcohol was selectively protected with TIPSCl, the olefin was cleaved by ozonolysis and the resultant aldehyde was protected as a 1,3-dioxolane. The 'masked' 1,3-dicarbonyl of the *m*-disubstituted arene was then ready to be revealed. As expected,[9] Birch reduction provided 1,4-cyclohexadiene **5** as a single regioisomer in 89% yield. Ozonolysis of the diene and reductive workup provided the crude 5-hydroxy-1,3-diketone which was directly dehydrated to give pyranone **6** in 43% yield over 2 steps.[9] Hydrogenation of **6** proceeded with good facial selectivity (dr = ~11:1). L-Selectride reduction of the resulting ketone provided the axial C_5-alcohol in 79% yield with a 12:1 diastereoselectivity. Subsequent silylation with TBDPSCl and transacetalization[10] with propane-1,3-dithiol led to dithiane **7**.

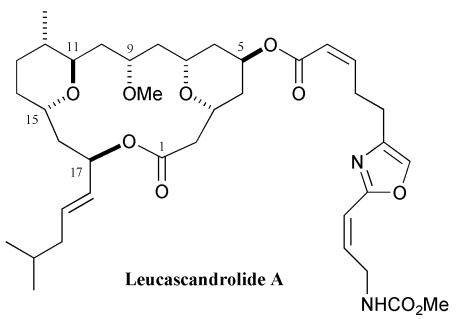
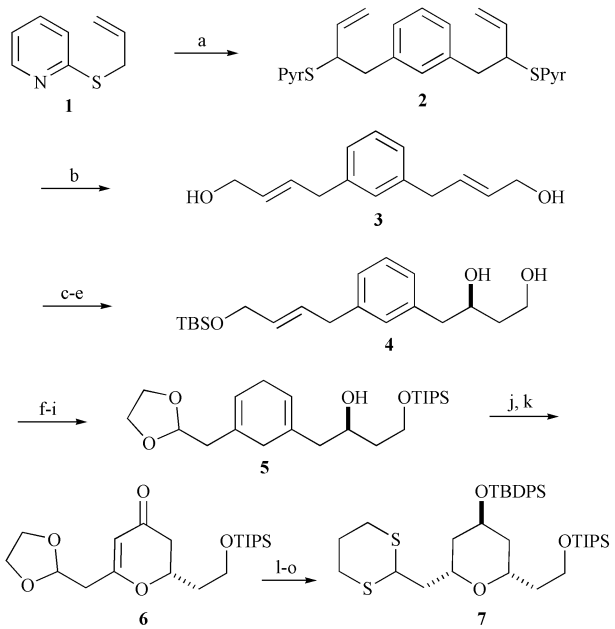


Fig. 1 Structure of Leucascandrolide A.

The synthesis of the C_{10}–C_{17} iodide began with the known silyloxyacetaldehyde **8**[11] (Scheme 2). Brown's *E*-crotylboration[12] provided the homoallylic alcohol in 55% yield as an 8:1 mixture of diastereomers. Attempted benzylation of this alcohol under standard conditions (NaH, BnBr, DMF or THF) resulted in significant (~40%) migration of the TBS group. Application of the conditions developed by Marshall[13] (*t*-BuLi, −78 °C; BnBr/HMPA) completely suppressed silyl migration to provide the desired benzyl ether in 86% yield. Ozonolysis of the olefin furnished the aldehyde in 74% yield. Wittig reaction led to benzyl ester **9**, which upon exposure to catalytic hydrogenation in EtOAc gave the lactone **10** in 87% yield. Partial reduction of the lactone carbonyl functionality with DIBAL-H and acetylation of the resultant lactol furnished the anomeric acetate in 87% yield as a 1.4:1 α:β mixture of anomers. Allylsilane addition[14] to this mixture of lactol acetates provided the tetrahydropyran **11** in 80% yield with excellent diastereoselectivity (15.6:1) favoring the desired axial isomer. Ozonolytic cleavage of the olefin gave the corresponding aldehyde which was subjected to a catalytic asymmetric vinylzinc addition reaction using conditions developed in our laboratories.[15] Thus, hydrozirconation of 4-methylpentyne, *in situ* transmetallation to the more reactive vinylzinc species, and addition of the aldehyde in the presence of 25 mol% of aminothiol ligand **12** provided the



Scheme 1 *Reagents and conditions*: (a) *n*-BuLi, THF, −78 °C; *m*-$(CH_2Br)_2C_6H_4$, 78%; (b) *m*-CPBA, MeOH; Et_2NH, 81%; (c) NaH, THF; TBSCl, 73% based on recovered **3**; (d) (−)-DIPT, Ti(*i*-PrO)$_4$, *t*-BuO_2H, 86%; (e) Red-Al, THF, −15 °C, 96%; (f) TIPSCl, im, CH_2Cl_2, 91%; (g) O_3, CH_2Cl_2, −78 °C; PPh_3; (h) $(CH_2OH)_2$, TsOH, PhH, reflux, 62% for two steps; (i) Li, NH_3, THF, −50 °C; $EtC(Me)_2OH$, 89%; (j) O_3, EtOAc, −78 °C; H_2, $Pd(OH)_2$; (k) TsOH, PhH, reflux, 43% for two steps; (l) H_2, Pd/C, EtOAc, 71%; (m) L-Selectride, THF, −78 °C, 79%; (n) TBDPSCl, im, DMAP, DMF, 83%; (o) $CH_2(CH_2SH)_2$, $TiCl_4$, CH_2Cl_2, 64%.

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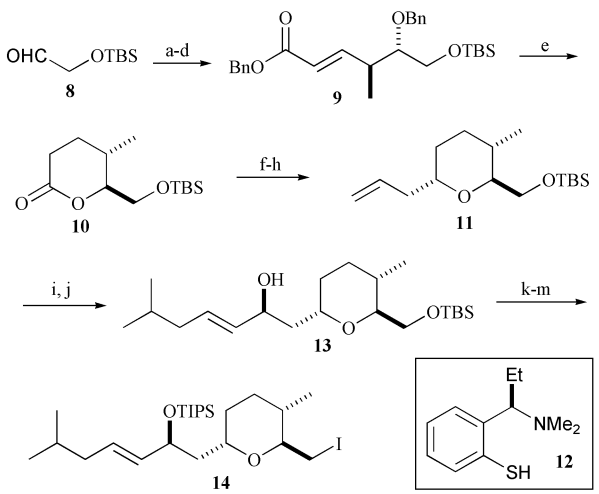
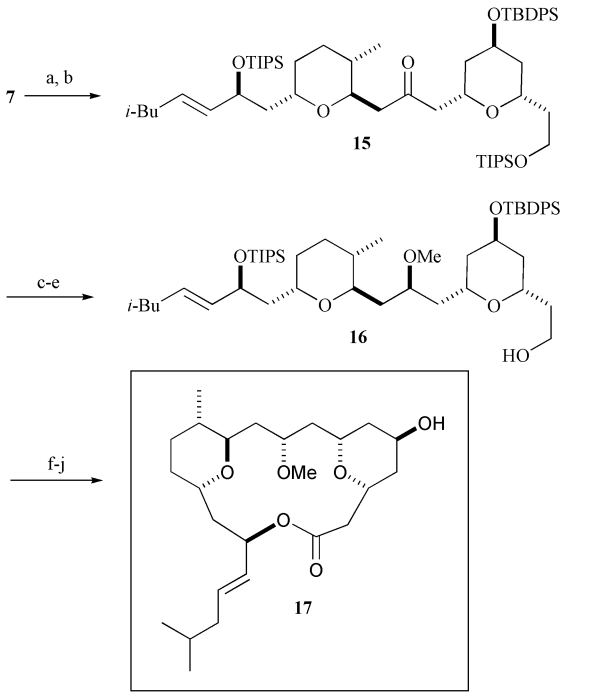


Scheme 2 *Reagents and conditions*: (a) (−)-Ipc_2B(*E*-crotyl), THF, Et_2O, −78 °C; NaOH, H_2O_2, 55%; (b) *t*-BuLi, THF, −78 °C; BnBr, HMPA, 86%; (c) O_3, CH_2Cl_2, −78 °C; PPh_3, 74%; (d) Ph_3PCHCO_2Bn, CH_2Cl_2, 63%; (e) H_2, Pd/C, EtOAc, 87%; (f) DIBAL-H, $PhCH_3$, −78 °C; (g) Ac_2O, pyr, 87% for two steps; (h) Allyl-TMS, BF_3OEt_2, CH_2Cl_2, −78 °C, 80%; (i) O_3, CH_2Cl_2, −78 °C; PPh_3, 86%; (j) 4-methylpentyne, $Cp_2Zr(H)Cl$, CH_2Cl_2; Me_2Zn, $PhCH_3$, **12** (25 mol%), −30 °C, 62%; (k) TIPSCl, im, DMAP, DMF, 76%; (l) EtOH, PPTS, 82%; (m) PPh_3, I_2, im, 87%.



Scheme 3 *Reagents and conditions*: (a) *t*-BuLi, THF/HMPA; **14**, 74%; (b) $PhI(O_2CCF_3)_2$, THF/MeOH/H_2O, 61%; (c) L-Selectride, THF, −78 °C, 98%; (d) MeOTf, 2-Me-4,6-(*t*-Bu)$_2$pyr., CH_2Cl_2, 93%; (e) EtOH, TsOH, 71%; (f) Dess-Martin periodinane, CH_2Cl_2; (g) $NaClO_2$, 2-methyl-2-butene, *t*-BuOH, THF, H_2O, 94% for two steps; (h) 1 M HCl, THF, 78%; (i) PPh_3, DIAD, THF, 0 °C, 58%; (j) TBAF, THF, 78%.

allylic alcohol **13** in 62% yield with a 5.1 : 1 diastereoselectivity. This ratio was initially assumed to be in favor of the desired C_{17} (*R*)-alcohol, *i.e.* the configuration which the chirality of the ligand and 1,3-chelate control by the substrate should both enforce. However, elaboration of the major diastereomer into an epimeric macrocycle proved that the vinylzinc addition actually favored the *opposite* C_{17} (*S*)-diastereomer. Accordingly, we changed our strategy to using a Mitsunobu macrolactonization[16] to rectify the C_{17} stereochemistry. Silylation of the secondary alcohol of the major diastereomer with TIPSCl followed by selective TBS deprotection under mildly acidic conditions and finally iodide formation provided the C_{10}–C_{17} fragment **14**.

Lithiation of dithiane **7** using the conditions developed by Williams[17] and addition of iodide **14** gave the C_1–C_{17} intermediate in 74% yield (Scheme 3). Dithiane deprotection[18] provided ketone **15**. Excellent diastereoselectivity was obtained in the reduction of this ketone with L-Selectride (98% yield, dr = 13.6 : 1). Methylation of the sterically hindered C_9-alcohol with methyl triflate and deprotection of the primary TIPS-ether provided alcohol **16**. Two step oxidation to the carboxylic acid using Dess-Martin periodinane followed by $NaClO_2$ proceeded in 94%. Removal of the secondary TIPS-ether with aqueous HCl in THF gave the C_{17}-*epi* seco acid in 78% yield. Gratifyingly, application of a slight modification of the conditions developed by Simon and coworkers[19] for Mitsunobu macrolactonization [syringe pump addition of the hydroxy acid to premixed PPh_3 (25 eq.) and DIAD (20 eq.) in THF at 0 °C] furnished the desired TBDPS-protected macrocycle in 58% yield. No products of allylic inversion or retention of configuration were detected in this reaction. Finally, desilylation with TBAF in THF provided the leucascandrolide A macrocycle **17**, which was identical in all respects with spectral data and specific rotations reported by Leighton,[2] Rychnovsky,[3] and Pietra.[1]

In conclusion, highlights of our formal total synthesis include the bidirectional synthesis of segment **4** and its elaboration into pyran **7** by arene reduction–diene ozonolysis. Furthermore, efficient thioacetal alkylation and Mitsunobu macrocyclization *via* inversion were used for segment coupling and lactonization. Work is in progress to elucidate the fundamental mechanism responsible for the unexpected doubly mismatched stereochemical outcome in the formation of the secondary allylic alcohol stereocenter at C_{17}.

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