Natural Product Synthesis

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A Sequential Two-Component Etherification/Oxa-Conjugate Addition Reaction: Asymmetric Synthesis of (+)-Leucascandrolide A Macrolactone **

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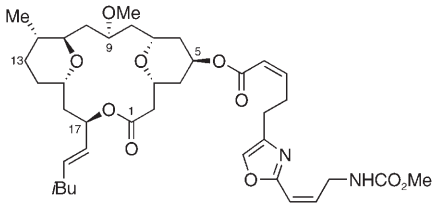
Dedicated to Professor Andrew B. Holmes on the occasion of his 65th birthday

Leucascandrolide A (**1**) is a novel macrolide possessing an unusual dioxotricyclic core, which displays potent cytotoxic activity against KB (throat epithelial cancer, $IC_{50} = 0.05\ \mu g\,mL^{-1}$) and P388 (murine leukemia, $IC_{50} = 0.25\ \mu g\,mL^{-1}$) tumor cell lines, in addition to antifungal activity against *Candida albicans*.[1] The latter feature is particularly important given the growing concern among AIDS patients with regard to infections from this animal-pathogenic yeast. Interestingly, the cytotoxic activity of **1** can primarily be attributed to the macrolide moiety, whereas the antifungal activity derives from the oxazole side chain. Hence, the ability to construct this agent in a more expeditious manner would provide the opportunity to conduct more detailed structure–activity studies and potentially capitalize on this divergent behavior. Although this agent was originally isolated from the calcareous sponge *Leucascandra caveolata* in the Coral Sea by Pietra and co-workers,[2] subsequent attempts to isolate the material have failed. This has led to speculation with respect to the actual source of this agent, which has tentatively been attributed to opportunistic bacteria colonizing a decayed portion of the sponge rather than a more classical symbiotic relationship. Hence, the unique molecular architecture and potent biological activity, coupled with the lack of bioavailability from natural sources, have inspired several outstanding syntheses of this important target.[3,4] Although these approaches have significant merit, both in terms of their strategic and methodological developments, they each construct the key 1,5-bis(tetrahydropyran) moiety in a stepwise manner.



(+)-leucascandrolide A (**1**)

Herein, we describe the most concise approach to leucascandrolide A (**1**) developed to date, by using a novel two-component etherification/oxa-conjugate addition reaction. It is anticipated that this strategy should be easily adapted to prepare related analogues of this important agent, which may provide insight into its mode of action. We envisioned the construction of the leucascandrolide A macrolactone (**2**) could be accomplished through macrolactonization of the seco acid **3** followed by removal of the benzyl group in an analogous manner to that described in a related approach (Scheme 1).[3] The seco acid **3** would be prepared from **4** through the stereoselective introduction of the alkenyl group to the aldehyde derived from the terminal alkene, and the reduction of the C9 ketone followed by methylation of the secondary alcohol. The 1,5-bis(tetrahydropyran) **4** would in turn be derived from reaction of the anomeric acetal **5** with the trimethylsilyloxy diene **6** via a one-pot diastereoselective sequential two-component etherification, followed by an oxa-conjugate addition. The anomeric acetal **5** and trimethylsilyloxy diene **6** required for the coupling would be readily available from the known enantiomeric β-hydroxy esters (*R*)- and (*S*)-**7**, respectively.

In a program directed towards the stereoselective construction of monocyclic ethers, we have developed a series of bismuth-mediated reactions for the construction of *cis*- and *trans*-2,6-disubstituted tetrahydropyrans.[5] A striking feature of this methodology has been the ability to develop multi-component etherification reactions, by using the rate of desilylation to orchestrate the cascade process. However, a critical requirement for the application of this strategy to the construction of the 1,5-bis(tetrahydropyran) core of leucascandrolide A is the ability to circumvent reversibility in the oxa-conjugate addition process so as to avoid complications with the epimerization of the *trans*-2,6-disubstituted tetrahydropyran ring. Although base-catalyzed variations are known

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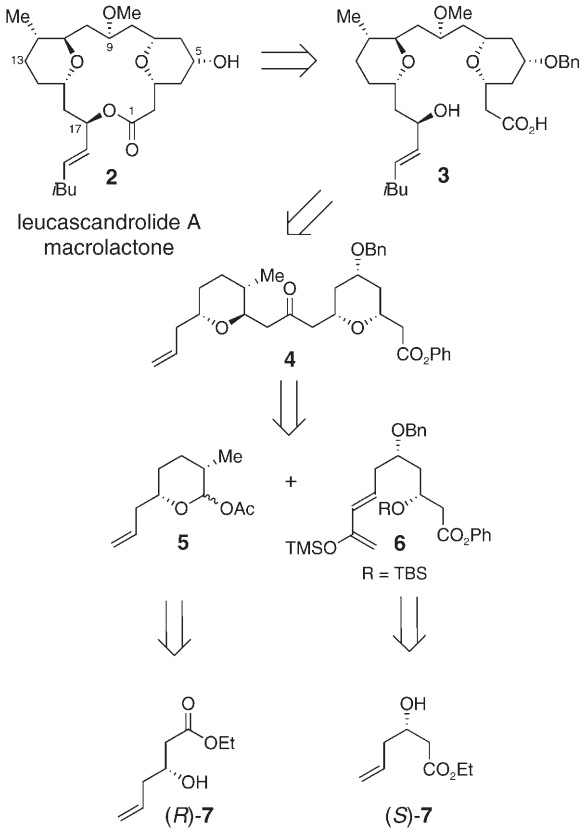
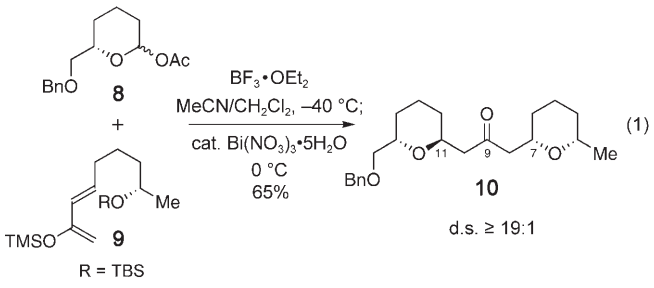
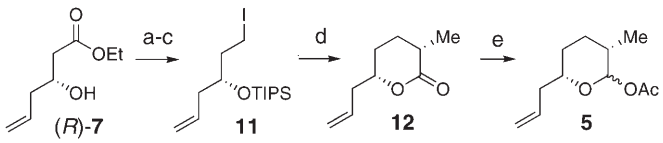


Scheme 1. Retrosynthetic analysis for (+)-leucascandrolide A macrolactone (**2**). Bn = benzyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

to proceed under thermodynamic control, we have recently demonstrated that the Brønsted acid catalyzed variation, using $Bi(NO_3)_3{\cdot}5H_2O$ as the acid source, minimizes reversibility making this approach now viable. Preliminary studies demonstrated the necessity for a dual Lewis and Brønsted acid catalyzed process to affect this type of sequential process. Treatment of the anomeric acetate **8** with the diene **9** (1.5 equiv) in the presence of $BF_3{\cdot}OEt_2$ at −40 °C followed by the addition of a catalytic amount of $Bi(NO_3)_3{\cdot}5H_2O$ and warming to 0 °C furnished the non-adjacent bis(tetrahydropyran) core **10** [Eq. (1)] in 65 % yield with ≥ 19:1 diastereoselectivity (by ^{1}H NMR spectroscopy). Additional support for the necessity of a Brønsted acid catalyzed oxa-conjugative addition was evident from the fact that the simple model system **10** undergoes base-catalyzed equilibration at C11.

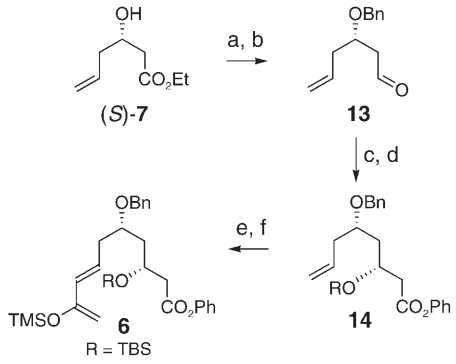


The synthesis of the anomeric acetate **5**, required for the left-hand fragment of leucascandrolide A, commenced from the known homoallylic alcohol (*R*)-**7**.[6] This is readily available from the regiospecific ring opening of commercially available ethyl (*S*)-oxiranyl acetate with the cuprate derived from vinylmagnesium bromide and copper bromide-dimethyl sulfide complex in 88 % yield.[7] The hydroxy group of (*R*)-**7** was protected as a triisopropylsilyl ether, then reduced with diisobutylaluminum hydride, and the primary alcohol converted into the primary alkyl iodide **11** in 90 % overall yield (Scheme 2). Asymmetric alkylation[8] of (1*R*,2*R*)-(−)-pseudoephedrine propionamide with **11** according to the procedure developed by Myers et al. was followed by in situ removal of the triisopropylsilyl group and acid-catalyzed lactonization to afford δ-lactone **12** in 72 % yield and with excellent diastereoselectivity (d.s. ≥ 19:1, by ^{1}H NMR spectroscopy).[9] Reduction of **12** with diisobutylaluminum hydride followed by in situ acylation of the lactol with acetic anhydride furnished anomeric acetate **5** in 88 % yield as a mixture of anomers (α/β = 5:1, by ^{1}H NMR spectroscopy).[10]



Scheme 2. Synthesis of the anomeric acetate **5**: a) TIPSOTf, imidazole, DMF, 0 °C→RT, 96 %; b) DIBAL-H, CH_2Cl_2, −40→−20 °C, 99 %; c) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C→RT, 95 %; d) (1*R*, 2*R*)-pseudoephedrine propionamide, LDA, LiCl, THF, −78→0 °C, **8**; then TBAF, PTSA, −10 °C→RT, 72 %; e) DIBAL-H, CH_2Cl_2, −78 °C, Ac_2O, pyridine, DMAP, 88 %. DIBAL-H = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamide, PTSA = *para*-toluenesulfonic acid, TBAF = tetrabutylammonium fluoride, Tf = triflate, TIPS = triisopropylsilyl.

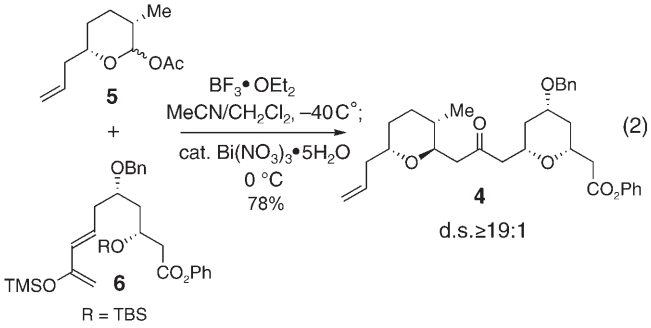
Scheme 3 outlines the synthesis of the trimethylsilyloxy diene **6**, which commenced with benzyl protection of the enantiomeric β-hydroxy ester (*S*)-**7**, followed by selective reduction of the ester to give aldehyde **13** required for the



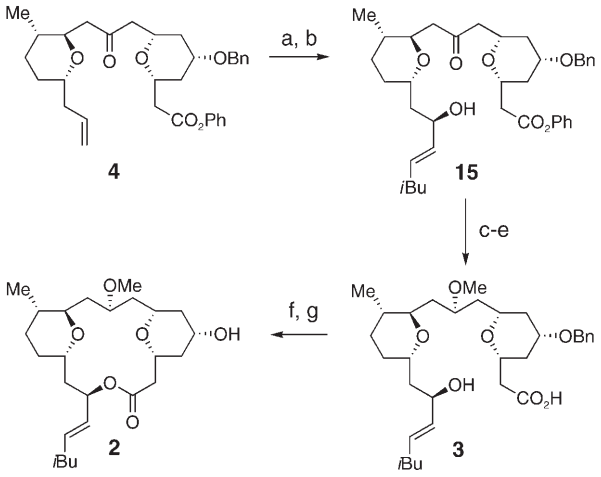
Scheme 3. Synthesis of the trimethylsilyloxy diene **6**: a) $PhCH_2Br$, Ag_2O, EtOAc, 89 %; b) DIBAL-H, CH_2Cl_2, −78 °C, 94 %; c) *N*-Ts-L-valine, $BH_3{\cdot}THF$, PhO(TMSO)C=CH_2, THF, −78 °C, 87 %; d) TBSOTf, imidazole, DMF, 0 °C→RT, 99 %; e) Hoveyda–Grubbs catalyst (5 mol %), CH_2=CHCOMe, (5 equiv), CH_2Cl_2, RT, 93 %; f) TMSOTf, Et_3N, THF, −78 °C→RT, 99 %. Ts = *para*-toluenesulfonyl.

asymmetric Mukaiyama aldol.[11] Treatment of the aldehyde **13** with the trimethylsilyl enol ether of phenyl acetate and *N*-tosyl-L-valine boron Lewis acid gave the corresponding β-hydroxy ester (d.s. = 15:1, by ^{1}H NMR spectroscopy), which was then protected to furnish the *tert*-butyldimethylsilyl ether **14** in 82% overall yield. The fragment was then completed by the conversion of the terminal olefin to the α,β-unsaturated ketone via a cross-metathesis reaction with methyl vinyl ketone,[12] followed by treatment with trimethylsilyl triflate and triethylamine to afford the trimethylsilyloxy diene **6** in 92% overall yield (Scheme 3).

The successful completion of the individual fragments provided an opportunity to examine the key one-pot diastereoselective sequential two-component etherification/oxa-conjugate addition reaction for the construction of the non-adjacent bis(tetrahydropyran) core of the natural product [Eq. (2)]. Gratifyingly, treatment of the anomeric acetate **5** with the diene **6** (1.5 equiv), in an analogous manner to that of the model study [Eq. (1)], furnished the non-adjacent bis(tetrahydropyran) core **4** in an improved 78% yield, with excellent diastereoselectivity (d.s. ≥ 19:1, by ^{1}H NMR spectroscopy).[5]



Scheme 4 outlines the completion of the (+)-leucascandrolide A macrolactone (**2**). Although the introduction of the alkenyl side chain initially proved problematic, a combination of the procedures developed by the research groups of Wipf and Walsh provided suitable reaction conditions for its installation.[13] Hence, ozonolysis of the terminal alkene of **4** gave the corresponding aldehyde, followed by treatment with the organozinc reagent derived from the hydrozirconation of 4-methylpentyne, in the presence of the (−)-MIB ligand, furnished the allylic alcohol **15** in 75% yield over two steps, after separation from the epimer (d.s. = 6:1, by ^{1}H NMR spectroscopy; Scheme 4).[14] Protection of the secondary alcohol of **15** with an acetate group followed by reduction[15] of the ketone afforded the desired alcohol with excellent selectivity (d.s. ≥ 19:1, by ^{1}H NMR spectroscopy). Methylation of the resulting secondary alcohol followed by in situ saponification of both the acetate and the phenyl ester provided seco acid **3** in 77% yield (over 3 steps). The seco acid **3** was converted into the macrolide using relatively standard transformations in accord with prior studies.[3] Yamaguchi macrolactonization[16] of the seco acid **3** followed by removal of the benzyl group furnished (+)-leucascandrolide A macrolactone (**2**) in 71% overall yield, thus completing our formal total synthesis of the natural product (see the Supporting Information). The spectroscopic data and optical rotation of (+)-leucascandrolide A macrolactone **2** was identical in all respects to the values reported in the literature [^{1}H/^{13}C NMR, IR, $[\alpha]_D^{24} + 46.2$ ($c = 0.39$, EtOH), lit.[1] $[\alpha]_D^{20} + 58$ ($c = 0.1$, EtOH)]. (+)-Leucascandrolide A (**1**) has previously been prepared from **2** by the introduction of the side chain through a Mitsunobu esterification at C5 in 78% yield.[3b]



Scheme 4. Completion of the total synthesis of (+)-leucascandrolide A macrolactone (**2**): a) O_3, $NaHCO_3$, CH_2Cl_2, −78 °C, then DMS, PPh_3, −78 °C→RT; b) *i*BuC≡CH, [Cp_2ZrHCl], CH_2Cl_2, −78 °C; then (−)-MIB, −10 °C, 75% (over 2 steps); c) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0 °C→RT, 91%; d) catecholborane, (*S*)-CBS, CH_2Cl_2, −78 °C; e) MeOTf, 2,6-di-*tert*-butylpyridine, RT; then $LiOH·H_2O$, H_2O, MeOH, THF, RT, 85% (over 2 steps); f) $Cl_3C_6H_2COCl$, Et_3N, DMAP, PhH, RT, 81%; g) DDQ (20 equiv), pH buffer, CH_2Cl_2, RT, 88%. Cp = cyclopentadienyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMS = dimethyl sulfide, (*S*)-CBS = (*S*)-methyl oxazaborolidine, MIB = morpholino isoborneol.

In conclusion, we have accomplished the asymmetric synthesis of (+)-leucascandrolide A macrolactone (**2**) by using a convergent 14-step sequence from the known (*S*)-β-hydroxy ester **7** in 20% overall yield, or 15 steps from the commercially available ethyl (*R*)-oxiranyl acetate in 18% overall yield. The combination of the two-component etherification and oxa-conjugate addition reactions provides the most convergent and efficient approach to the non-adjacent tetrahydrofuran core and ultimately leucascandrolide A (**1**) developed to date. We anticipate that this strategy will facilitate structure–activity relationship studies to further delineate the intriguing dichotomy in biological activity.

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