Natural Products

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Oxidative Cleavage in the Construction of Complex Molecules: Synthesis of the Leucascandrolide A Macrolactone**

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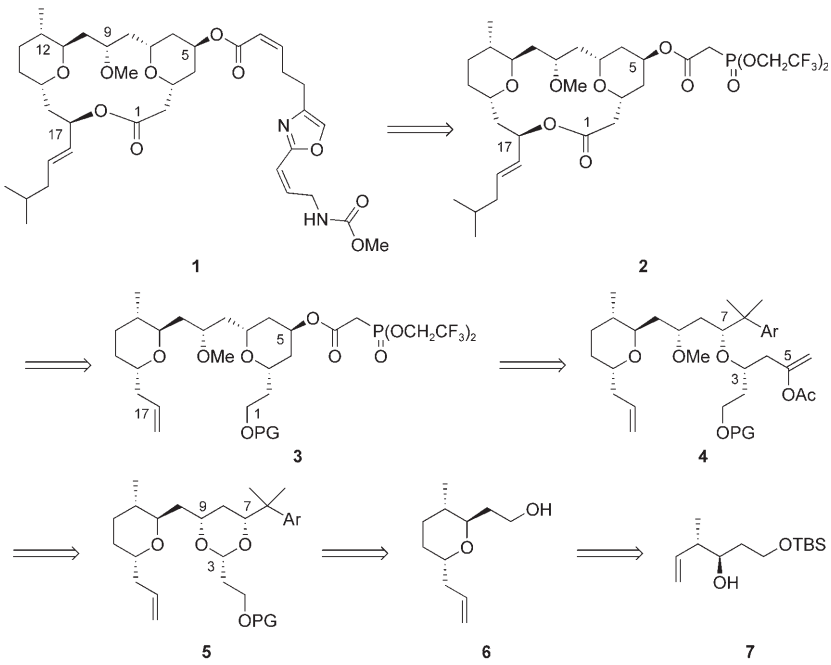
Dedicated to Professor Frederick E. Ziegler on the occasion of his retirement

Leucascandrolide A (**1**) is a potent cytotoxic and antifungal macrolide that was isolated by Pietra and co-workers from the New Caledonian sponge *Leucascandra caveolata*.[1] Subsequent efforts to isolate the natural product were unsuccessful,[2] leading to speculation that the actual source of **1** is an as yet unidentified bacterial symbiont. Based on its biological activity, inaccessibility from natural sources, and ample synthetic challenges, the construction of leucascandrolide A has generated substantial interest, resulting in several total and formal syntheses.[3] Our interest in **1** arose from studies in which we demonstrated that 2,6-*cis*-dialkyltetrahydropyran-4-ones, relevant to the C_3–C_7 portion of **1**, can be prepared through efficient oxidative cleavage reactions of homobenzylic ethers.[4] Herein we report the synthesis of leucascandrolide A, which is the first application of our electron-transfer-initiated cyclization (ETIC)[5] method for natural-product synthesis. In addition, the sequence described herein has been designed to minimize the use of protecting groups and reagent-based stereoinduction, resulting in an efficient approach with respect to linear and overall step counts.



Scheme 1. Retrosynthetic analysis of leucascandrolide A (**1**). TBS = *tert*-butyldimethylsilyl, OAc = acetate, PG = protecting group, Ar = *p*-methoxyphenyl.

Our target in this study (Scheme 1) was phosphonate **2**, which has been converted into **1** in one step by Leighton and co-workers.[3a] The lactone can be crafted from **3** through a sequence in which the introduction of the C_{17} allylic alcohol group required caution, owing to the presence of the labile C_5 phosphonoester. We envisioned the 2,6-*cis*-dialkyltetrahypropyran structure as arising from the single-electron oxidation, fragmentation, and cyclization of **4**. The challenging ether linkage between C_3 and C_7 can be prepared through nucleophilic opening of acetal **5**. Tetrahydropyran **6**, which can be accessed from alcohol **7**, was selected as the precursor to **5**. Alcohol **7** can be prepared in high enantiomeric purity through a reported[6] three-step sequence from 1,3-propanediol that utilizes a Brown crotylation reaction[7] to establish relative and absolute stereochemical control.

We explored hydroformylation reactions in an effort to access a tetrahydropyran group in one step from **7** (Scheme 2). As we wanted to avoid protecting groups and harsh reaction conditions, we employed Breit and co-workers' conditions[8] (step (a) in Scheme 2) for this transformation. This remarkably simple procedure (H_2 and CO can be introduced individually through separate balloons, obviating the need to purchase syngas) provided lactol **8** in 90% yield. Exposing **8** to allyl trimethylsilane and $BiBr_3$[9] at room temperature resulted in the direct formation of tetrahydropyranyl alcohol **6** as a single stereoisomer in nearly quantitative yield within 20 minutes. This reaction proceeded through the instantaneous formation of an isolable bridged bicyclic acetal, arising from the addition of the silyloxy group into the intermediate C_{15} oxocarbenium ion, followed by a

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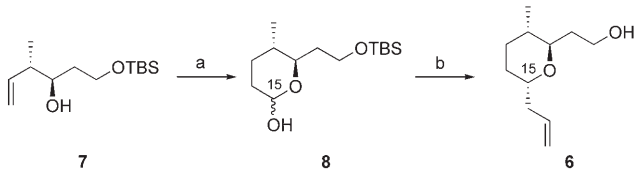
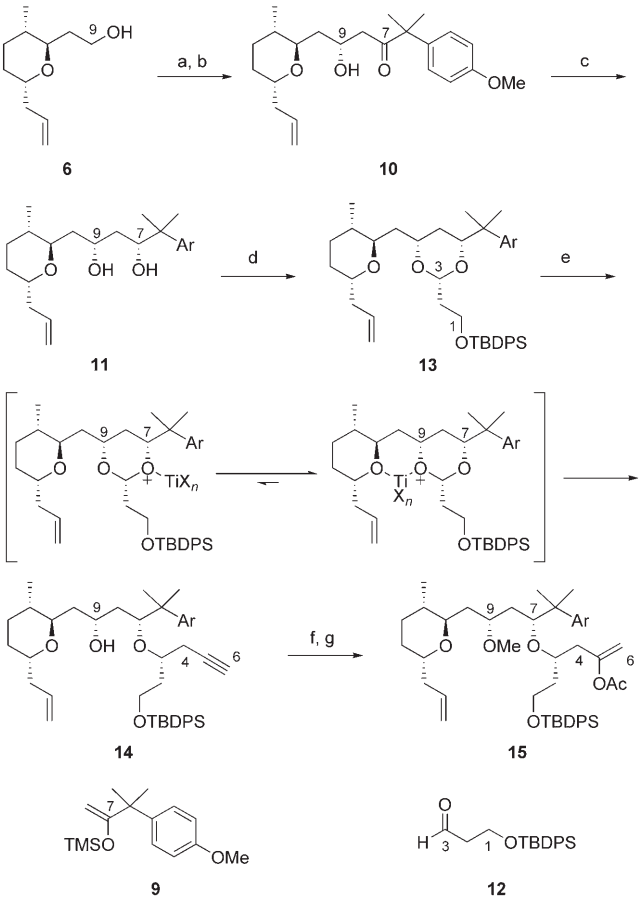


Scheme 2. Tetrahydropyran synthesis. a) H_2, CO, $[Rh(CO)_2acac]$, 6-diphenylphosphino-2-pyridone, THF, 1 atm, RT, 90% yield. b) Allyl trimethylsilane, $BiBr_3$, CH_3CN, RT, 99% yield. TBS = *tert*-butyldimethylsilyl, acac = acetylacetonyl.

second ionization that allowed for allyl group incorporation. These conditions promote direct nucleophilic substitutions of lactols and avoid cryogenic conditions without sacrificing efficiency or stereocontrol.

The electroauxiliary for the key ETIC reaction was introduced (Scheme 3) through a sequence of alcohol oxidation and $BF_3{\cdot}OEt_2$-mediated Mukaiyama aldol addition[10] of enolsilane **9**[11] to form ketone **10** as an inseparable 4.5:1 mixture of diastereomers. The stereochemical assignment at

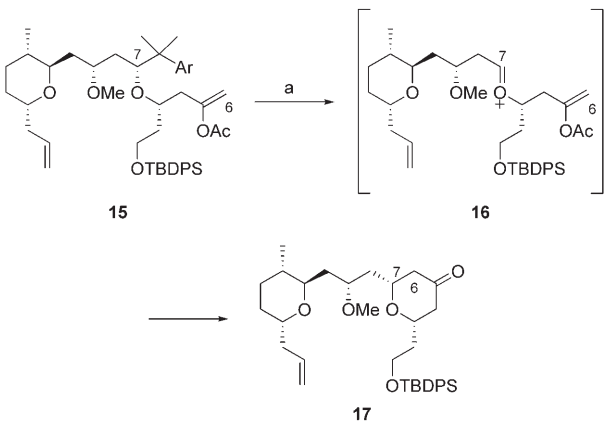


Scheme 3. ETIC substrate synthesis. a) Dess–Martin periodinane, pyridine, CH_2Cl_2. b) **9**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 78% yield (two steps), d.r. = 4.5:1. c) $NaBH_4$, Et_2BOMe, MeOH, THF, then NaOOH, 76% yield. d) 1) TMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C. 2) **12**, TMSOTf, CH_2Cl_2, −78–45 °C, 87% yield. e) Allenyltributyltin, $TiCl_4/Ti(O\mathit{i}Pr)_4$ (3:1), CH_2Cl_2, −78 °C, 89% yield. f) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 87% yield. g) HOAc, $[Ru(p\text{-cymene})Cl]_2$, $(2\text{-furyl})_3P$, Na_2CO_3, toluene, 72% yield. TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

C_9 in the major product was made using the literature precedent[12] regarding outcomes of Lewis acid-mediated additions into β-alkoxyketones. Higher diastereocontrol (7.8:1) was observed when the solvent was changed from CH_2Cl_2 to toluene, but the overall yield was lower (50%). Selective *syn*-reduction with $NaBH_4$ and Et_2BOMe[13] gave diol **11**, which could be isolated in 76% yield as a single stereoisomer. The C_1–C_3 fragment was incorporated by acetalization[14] that proceeded through the formation of the bis(trimethylsilyl) ether of **11** followed by the addition of aldehyde **12**[15] and TMSOTf[16] to yield **13**. The C_4–C_6 subunit was then incorporated by a Lewis acid-mediated acetal opening[17] in the presence of allenyltributyltin, thereby completing the construction of the requisite ether linkage for the oxidative cyclization reaction. Regioselective formation of the C_9 hydroxy group in this reaction results from Lewis acid chelation between the C_9 and C_{11} oxygen atoms and from the sterically disfavored interaction with geminal methyl groups on the electroauxiliary that arises from Lewis acid coordination to the C_7 oxygen atom. The synthesis of cyclization precursor **14** was completed by C_9 methyl ether formation and ruthenium-mediated Markovnikov addition of acetic acid across the alkyne.[18]

The key ETIC reaction progressed quite smoothly, with **15** being treated with ceric ammonium nitrate at room temperature to form tetrahydropyranone **17** as a single stereoisomer (Scheme 4). This reaction proceeded through oxidative cleavage of the benzylic carbon–carbon bond to form oxocarbenium ion **16**, with the excellent diastereoselectivity arising from the much-precedented[19] chair transition state for *endo*-cyclizations of this type.

With the two tetrahydropyran rings in place, we turned our attention to completing the synthesis of the macrocycle (Scheme 5). To move closer to this objective we needed to reduce the C_5 ketone. Although both diastereomers of the C_5 alcohol have been converted into the natural product,[3] we opted to proceed through the axial alcohol. Thus **17** was reduced with L-Selectride[20] to provide **18** in 76% yield along with 8% of the equatorial alcohol. Rather than capping the resulting alcohol with a protecting group we converted **18** into phosphonoacetate **19** using $(CF_3CH_2O)_2P(O)CH_2CO_2H$[21]



Scheme 4. ETIC reaction. a) Ceric ammonium nitrate, 4-Å M.S., $NaHCO_3$, 1,2-dichloroethane, CH_3CN, 68%.

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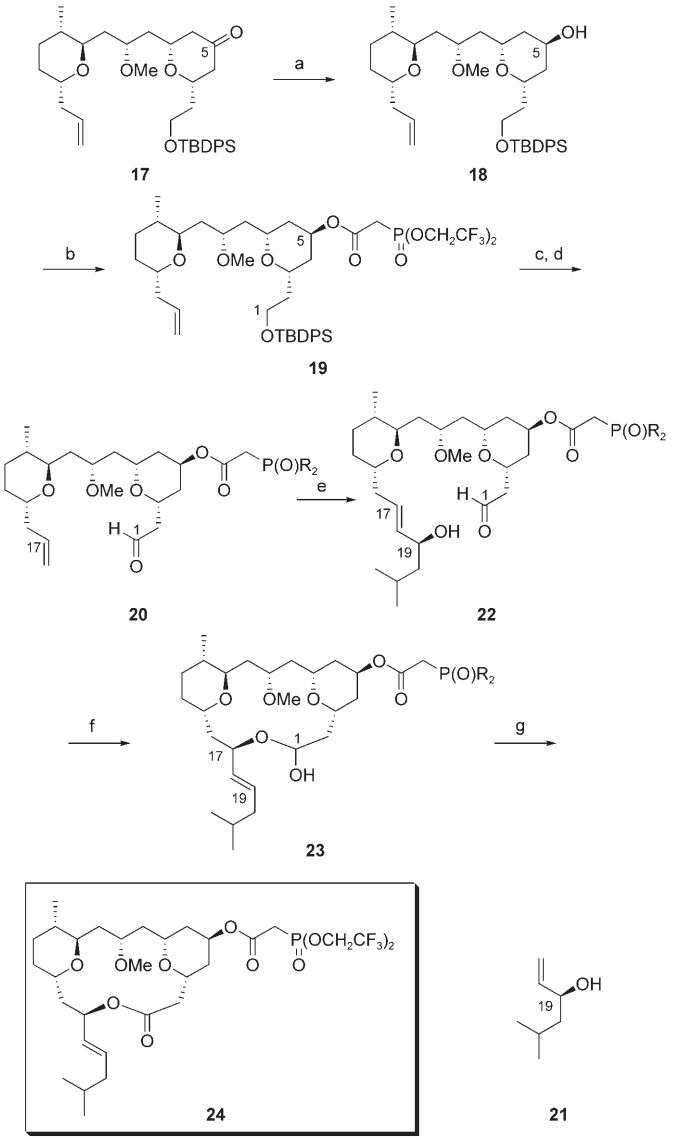

Scheme 5. Completion of the synthesis. a) L-Selectride, THF, −90 °C, 76%. b) $(CF_3CH_2O)_2P(O)CH_2CO_2H$, EDC, HOBt, CH_2Cl_2, 92%. c) HCl, MeOH, 98%. d) Dess-Martin periodinane, CH_2Cl_2, 95%. e) **21**, Hoveyda–Grubbs catalyst, 1,4-benzoquinone, CH_2Cl_2, reflux, 70%. f) Re_2O_7, Et_2O, 69%. g) PCC, CH_2Cl_2, 81%. EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HOBt = 1-hydroxybenzotriazole, PCC = pyridinium trioxochlorochromate, R = OCH_2CF_3.

and EDC with the expectation that this group would ultimately be used for the construction of the C_5 side chain through a Still–Gennari reaction.[22] The presence of the electrophilic phosphonate group, however, required us to complete the synthesis under very mild conditions. Silyl group cleavage was achieved with hydrochloric acid in methanol, with no phosphonate transesterification being observed. Notably, attempts to conduct this reaction with fluoride sources promoted the cleavage of one trifluoroethoxy group from the phosphonate group. Oxidation of the resulting alcohol with the Dess–Martin periodinane[23] yielded aldehyde **20**. A cross-metathesis reaction[24] between **20** and **21**[25] using the Hoveyda–Grubbs catalyst[26] provided allylic alcohol **22** in 70% yield. Adding *p*-benzoquinone to this reaction proved to be useful in suppressing ketone formation through alkene isomerization.[27] At this stage allylic alcohol transposition was required prior to macrolide formation. While **22** and the product of its transposition are both secondary allylic alcohols, we postulated that the desired transposed product would be formed preferentially under equilibrating conditions. This assertion was based on the capacity for the transposed hydroxy group to engage in hydrogen bonding with the tetrahydropyranyl ether and, in consideration of Kozmin and co-workers' report[3f] of the unexpected stability of the leucascandrolide macrolactol, for its potential to add into the pendent C_1 carbonyl group. Thus we exposed **22** to Re_2O_7 in Et_2O, conditions shown by Lee and Hansen[28] to promote suprafacial migration, thereby transposing the allylic alcohol group and forming lactol **23** directly in 69% yield. Notably, we observed that subjecting the C_{19}-epimer of **22**, prepared through the cross metathesis of **20** with the enantiomer of **21**, to the transposition conditions provided **23** in 49% yield. This result suggests that epimerization can occur during the transposition and that resolving **21** prior to metathesis is not necessary. While the reason for the epimerization has yet to be determined, we speculate that the transposition is rapid and reversible, and that rearrangement occasionally proceeds through a boat-like rather than a chair-like transition state. Oxidizing **23** with PCC completed the synthesis of leucascandrolide macrolactone **24**. Since **24** has been converted in one step into leucascandrolide A by the Leighton group, this completes a formal synthesis. Cleaving the phosphonoacetate group (Na_2CO_3, MeOH) provided a C_5 alcohol that is spectroscopically identical to material that was derived from cleaving the ester side chain from **1**,[1] thereby confirming the structural assignment.

We have completed a concise formal synthesis of leucascandrolide A through a sequence in which our ETIC method was employed for the stereoselective formation of a key tetrahydropyran ring from an advanced intermediate, thereby establishing the utility of the method in the context of complex molecule construction. Additional noteworthy advances include the minimization of protecting group manipulations (only two steps in the longest linear sequence were solely devoted to functional group protection or deprotection), the use of $BiBr_3$ in a mild and efficient lactol functionalization, the extensive use of substrate-derived stereocontrol, and the utilization of macrolactol formation as a thermodynamic driving force for allylic alcohol transposition. The sequence proceeds in 17 linear steps from the known alcohol **7** (20 steps from commercially available material) and in 4.5% yield, making this route quite competitive with the most efficient enantioselective routes to leucascandrolide A.

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