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Leucascandrolide A: Synthesis and Related Studies

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The total synthesis of the biologically active marine natural product leucascandrolide A is reported. A convergent strategy is employed, allowing for the rapid assembly of the macrolide moiety. Key steps of our approach include the diastereoselective addition of a zinc alkynilide to (*R*)-isopropylidene glyceraldehyde, the enantioselective copper(I) fluoride catalyzed aldol addition of a TMS-dienolate to crotonaldehyde, and the formation of a 2,6-trans-substituted tetrahydropyran by selenium-mediated intramolecular cyclization. Moreover, dramatic solvent effects observed in the macrolactonization reaction suggest that hydrogen-bonding effects play a critical role. An improved route to a key intermediate of our synthesis is documented.

Introduction

Over the past few decades, marine organisms have emerged as a rich source of natural products displaying potent biological activity. A myriad of diverse structures with, in some cases, fascinating physiological properties, have been isolated.[1] One important class of these natural products are represented by macrolides[2] such as the spongistatins[3] and bryostatins.[4]

In 1996, Pietra and co-workers reported the characterization of leucascandrolide A (**1**),[5] a powerfully bioactive marine macrolide isolated from a calcareous sponge of a new genus, *Leucascandra caveolata* Borojevic and Klautau, collected in 1989 along the east coast of New Caledonia (Figure 1). Leucascandrolide B (**2**), isolated from the same sponge, displays few structural similarities and significantly reduced bioactivity relative to **1**.[6]

Although leucascandrolide A was isolated in significant amounts (70 mg of **1** from 240 g of sponge, 0.03%), later expeditions, aimed at isolating additional quantities of **1**, only harvested samples of the sponge that failed to provide the natural product. The origin of this polyacetate-derived natural product still remains a puzzle, but it is most likely microbial. The fact that samples of *Leucascandra caveolata* collected in 1994 did not contain any trace of **1** or **2** suggests that the earlier sample was colonized by microorganisms that were the source of these macrolides.

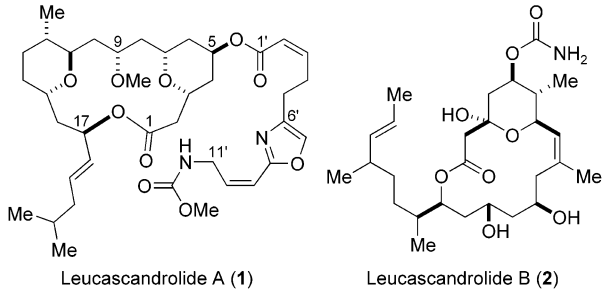

FIGURE 1. Structures of Leucascandrolide A (**1**) and B (**2**).

Leucascandrolide A is the first powerfully bioactive metabolite isolated from a calcareous sponge. The raw extracts from the sponge collected in 1989 are strongly antimicrobial and cytotoxic. The purified compound displays strong cytotoxic activity in vitro on human KB throat epithelial cancer cell lines (IC_{50} 0.05 μg/mL) and P388 murine leukemia cell lines (IC_{50} 0.25 μg/mL). Its antifungal properties are demonstrated by growth inhibition of *Candida albicans*, a pathogenic yeast that opportunistically attacks AIDS patients. Structure−activity relationship studies indicate that the C5 side chain has no major impact on the cytostatic properties. However, this structural element proved to be essential for the antifungal properties.

The gross structure and relative configuration of leucascandrolide A were assigned on the basis of HR-EI-MS, ^{13}C NMR, and DEPT experiments, as well as elaborate two-dimensional NMR studies. The absolute configuration could be determined by Mosher-ester analysis.[7]

As can be seen from Chart 1, leucascandrolide A displays several distinctive architectural features: the structure is characterized by a repeating 1,3-dioxygen-

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(3) For a review on spongistatins, see: Pietruszka, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2629−2636.

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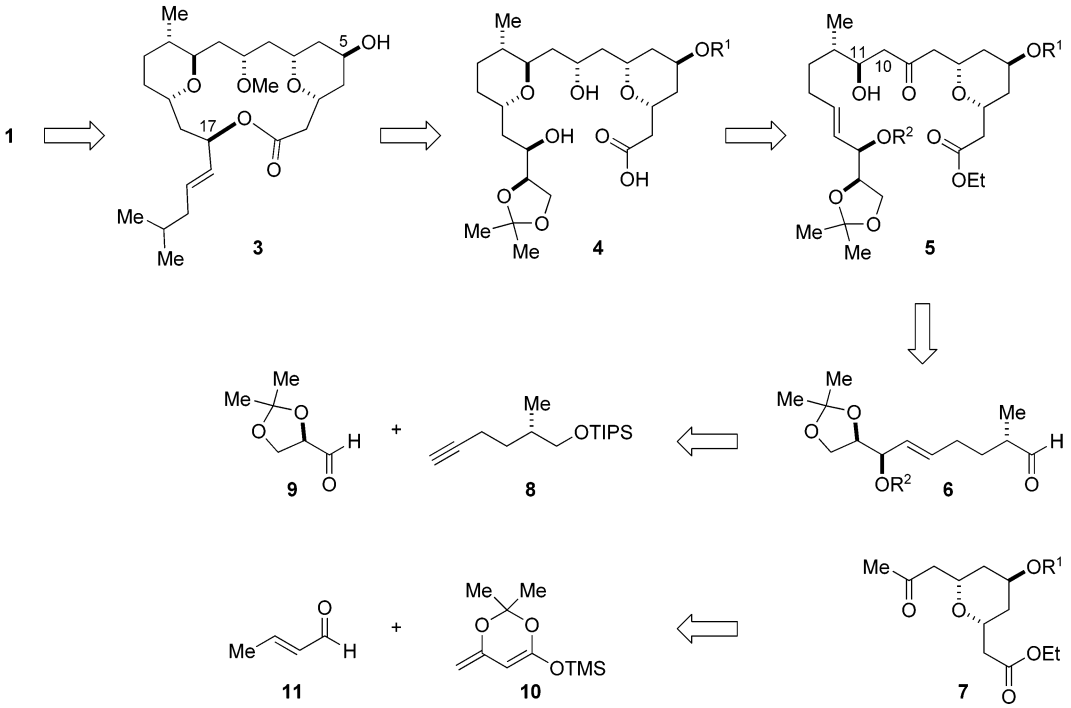

FIGURE 2. Retrosynthetic approach.

ation pattern, a peculiar side chain bearing a 2,4-disubstituted oxazole, and an 18-membered macrolactone that encompasses two trisubstituted tetrahydropyrans, one of which is 2,6-trans-disubstituted.

Because the biological origin of leucascandrolide A is currently unknown, total synthesis is its only reliable source. Accordingly, considerable efforts toward its synthesis have been made by several groups, including our own, culminating in the first total synthesis reported by Leighton, confirming the relative and absolute stereochemical configuration originally proposed by Pietra.[8] Elegant syntheses by Rychnovsky,[9] Wipf,[10] Kozmin,[11] and Paterson[12] have also been documented. Additionally, interesting studies by Crimmins,[13] Hoffmann,[14] O'Doherty,[15] and Panek[16] underline the importance and appeal of this natural product.

The lack of availability of leucascandrolide A from natural sources and its potent biological profile, as well as recent methodological developments in our group, compelled us to initiate a program aiming at the synthesis of this architecturally unique macrolide. We now report an improved total synthesis of leucascandrolide A, as well as a full account of our studies and observations, leading to its convergent and expedient synthesis.[17]

Synthesis Plan

Our retrosynthetic planning, outlined in Figure 2, was chosen on the basis of convergence and synthetic flexibility. Initial scission of the C5 side chain provides the leucascandrolide A macrolide **3**, containing the entirety of stereogenic centers found in the natural product. The proposed late-stage introduction of the C17 side chain would allow for expedient access to leucascandrolide A analogues and avoid problems associated with chemoselectivity in the route. Macrocyclization was intended to proceed by lactonization of ω-hydroxy acid **4**. Retrosynthetic unraveling of the 2,6-trans-disubstituted tetrahydropyran gave a 6-hydroxy olefin, a transformation that was planned, in the synthetic direction, to proceed by electrophile-mediated cyclization. The cyclization precursor would be formed by a convergent, diastereoselective boron-aldol addition reaction to form the C10−C11 bond in **5**. This approach delimits the synthetic challenge to the preparation of two key intermediates of comparable size and stereochemical complexity: aldehyde **6** and methyl ketone **7**. Our synthesis of **6** is based on the diastereoselective addition of alkyne **8** to (*R*)-isopropylidene glyceraldehyde (**9**) mediated by (−)-*N*-methyl ephedrine and zinc triflate using a protocol recently developed in our group for the mild and asymmetric addition of alkynes to aldehydes. Methyl ketone **7** derives from TMS-dienolate **10** by enantioselective aldol addition to crotonaldehyde (**11**).

(8) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894−12895.
(9) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420−8421.
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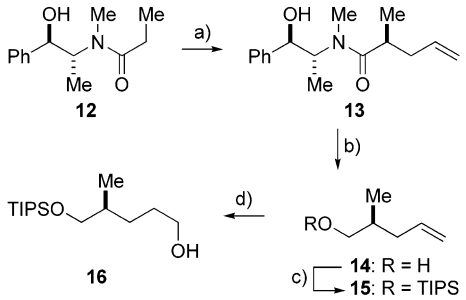
Results and Discussion

The synthesis of leucascandrolide A commenced with the preparation of known alcohol **16** from (1*R*,2*R*)-(−)-pseudoephedrine propionamide **12** by a high-yielding, four-step reaction sequence reported by Bode and Carreira in the course of their total syntheses of epothilone natural products[18] (Scheme 1). Asymmetric alkylation of the lithium enolate of **12** with allyl iodide, using the protocol reported by Myers,[19] gave amide **13** (dr > 95:5 by ^{1}H NMR). Subsequent BH_3·NH_3-mediated reduction led to alcohol **14**, which was protected as a triisopropylsilyl ether under standard conditions. Hydroboration of the monosubstituted double bond in **15** with 9-BBN gave the desired compound **16** in 75% yield over four steps.

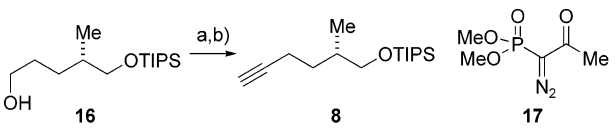
SCHEME 1[a]



[a] Reaction conditions: (a) LDA, LiCl, allyl iodide, THF, −78 °C → 0 °C, 2 h (dr > 95:5); (b) LDA, NH_3·BH_3, THF, rt, 2 h; (c) TIPSCl, imidazole, DMAP, rt, 1 h; (d) 9-BBN, THF, rt, 6 h, 75% over four steps.

Oxidation of the primary alcohol in **16** to the corresponding aldehyde was conveniently achieved with the biphasic NaClO/TEMPO/KBr system[20] (Scheme 2). Conversion to the terminal alkyne **8** could be carried out by various methods. Addition of lithiated trimethylsilyl diazomethane[21] was found to give the best yields (90% over two steps). On a large scale, however, the use of the Ohira reagent[22] (**17**) using the protocol reported by Bestmann[23] was the method of choice and gave alkyne **8** in 87% yield over two steps.

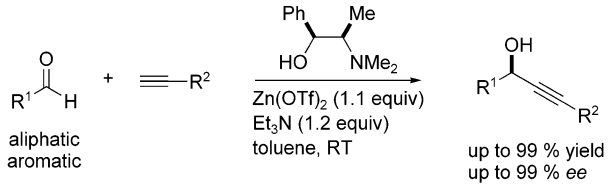
SCHEME 2[a]



[a] Reaction conditions: (a) aq NaClO, TEMPO (2.0 mol %), KBr (10 mol %), CH_2Cl_2, pH 8.6 carbonate buffer, 0 °C, 15 min; (b) $(MeO)_2P(O)CN_2CO_2CH_3$, K_2CO_3, MeOH, 16 h, rt, 87% (over two steps).

The total synthesis of leucascandrolide A provided the opportunity to investigate whether zinc acetylide additions (Scheme 3) could be carried out with highly functionalized aldehydes on preparatively useful scales. Additionally, our previous studies in this area had left unexplored the use of chiral aldehydes as substrates leading to the formation of diastereomeric propargylic alcohols.[24]

SCHEME 3



The synthetic route called for the use of (*R*)-isopropylidene glyceraldehyde (**9**) and optically active alkyne **8**. Although the remote stereogenic center in the alkyne was not expected to bias the diastereofacial differentiation in the aldehyde, the situation was far less clear as it concerned the chiral aldehyde. Of additional importance was the question of whether isopropylidene glyceraldehyde would be compatible with the reaction conditions; the use of this capricious aldehyde would constitute a notable and useful extension of the method.

The zinc alkynilide of **8**, prepared in situ by reaction of **8** with $Zn(OTf)_2$ (1.1 equiv), (−)-*N*-methyl ephedrine (1.1 equiv), and Et_3N (1.2 equiv), cleanly added to aldehyde **9**[25] to give propargylic alcohol **18** in 75% yield and 94:6 diastereoselectivity as assayed by ^{1}H NMR, favoring the 1,2-syn configuration (Scheme 4).[26] In the course of finding optimal conditions, we noted that the use of high-purity isopropylidene glyceraldehyde **9** proved to be crucial to the formation of addition product **18** in high yield and diastereoselectivity. When (+)-*N*-methyl ephedrine was used, under otherwise identical conditions, the product possessing a 1,2-anti relationship was ob-

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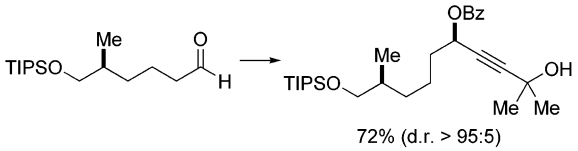
(24) Addition of a chiral aldehyde possessing a remote stereocenter to 3-methyl-butyn-3-ol was reported by Carreira and Bode in the recently published epothilone A synthesis. See ref 18b for details.



(25) (*R*)-Isopropylidene glyceraldehyde (**9**) was prepared in two steps from D-mannitol and distilled immediately prior to use: Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056−4058.

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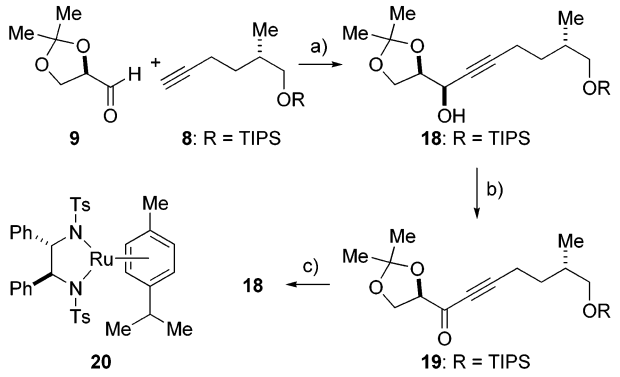
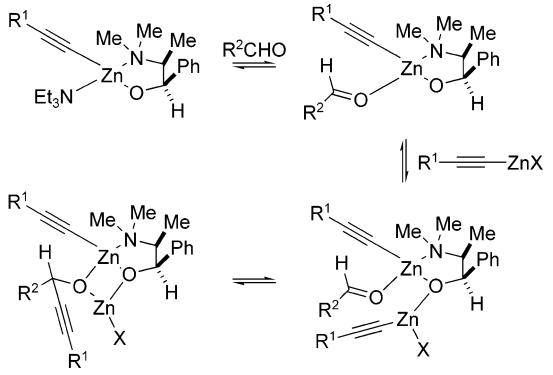
SCHEME 4[a]



[a] Reaction conditions: (a) **8**, $Zn(OTf)_2$, (−)-*N*-methyl ephedrine, Et_3N, toluene, then **9**, rt, 48 h, 75% (dr = 94:6); (b) 4 Å MS, NMO, CH_2Cl_2, then TPAP, rt, 30 min, 75%; (c) **20**, *i*PrOH, rt.

SCHEME 5

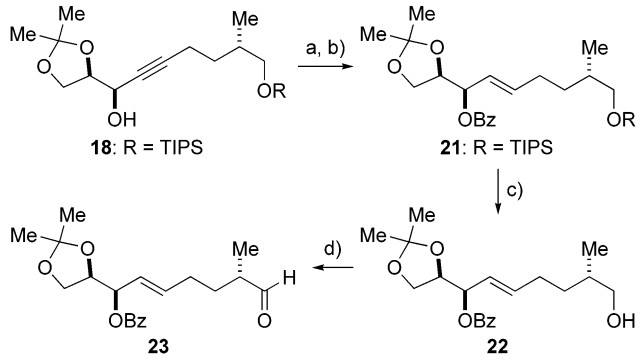


tained as the sole diastereomer, indicating that reagent control is dominant in this addition.[27] The lack of diastereoselectivity observed with the corresponding lithium alkynilide underscores the significance of these results.[28] The sense of stereochemical induction was confirmed by oxidation of **18** to ketone **19** (TPAP, NMO, 4 Å MS, CH_2Cl_2, 75%)[29] and subsequent asymmetric transfer hydrogenation to **18** using Noyori's catalyst[30] **20**.

The stereochemical outcome of the addition process can be rationalized by the mechanistic pathway represented in Scheme 5.[31] The model is analogous to that proposed by Noyori for diethyl zinc additions to aldehydes;[32] two metal centers operate synergistically in a highly organized transition state wherein both electrophilic and nucleophilic components are activated.

Reduction of propargylic alcohol **18** to the corresponding (*E*)-allylic alcohol using $LiAlH_4$[33] followed by benzoylation under standard conditions (BzCl, Et_3N, CH_2Cl_2) gave **21** in 90% yield over two steps (Scheme 6). Deprotection of the silyl ether[34] with nBu$_4$NF (96%) and subsequent Ley oxidation[29] (TPAP, NMO, 4 Å MS, CH_2Cl_2) of the resulting alcohol **22** furnished aldehyde **23** in 87% yield. Under these mild oxidation conditions, no epimerization α to the aldehyde took place. The synthesis outlined proceeds in seven steps and 49% overall yield from **16**.

SCHEME 6[a]



[a] Reaction conditions: (a) $LiAlH_4$, THF, rt, 5 h; (b) BzCl, Et_3N, DMAP, CH_2Cl_2, rt, 15 h, 90% (over two steps); (c) nBu$_4$NF, THF, 0 °C → rt, 24 h, 96%; (d) 4 Å MS, NMO, CH_2Cl_2, then TPAP, rt, 30 min, 87%.

In the synthesis of the second key intermediate, we were interested in investigating whether the catalytic, enantioselective addition of dienolate **10** to aldehydes using the (*R*)-Tol-BINAP copper(I) fluoride complex was amenable to the preparation of aldol adduct **24** on a multigram scale.[35] This would require the use of crotonaldehyde as an electrophile, an aldehyde that has been shown to be prone to polymerization under similar reaction conditions. The catalyst is conveniently prepared in situ from (*R*)-Tol-BINAP, copper(II) triflate, and nBu$_4$NPh$_3$SiF$_2$[36] (Scheme 7).

This reaction can be conducted on a multigram scale utilizing as little as 2 mol % catalyst.[37] Dioxenone **24** was obtained with a high degree of enantioselectivity (91% ee as determined by HPLC) and 44% yield. Conversion of aldol adduct **24** to keto ester **26** was achieved by thermal retro-Diels−Alder reaction leading to acetone extrusion and subsequent trapping of intermediate ketene **25** with solvent 1-butanol (78%) (Scheme 8).[38]

(27) A similar result was obtained with (2*S*)-2-(*tert*-butyldimethylsilyloxy)-propanal: El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017−3020.

(28) Additions of lithium acetylides to this aldehyde are known to be fairly nonselective: Kang, S. H.; Kim, W. J. *Tetrahedron Lett.* **1989**, *30*, 5915−5918.

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(33) Pronounced inverse correlation between the Lewis basicity of the solvent and the extent of cis reduction was observed: (*E*)-olefins are obtained in THF and *E*/*Z* mixtures in Et_2O. For a possible rationale, see: (a) Grant, B.; Djerassi, C. *J. Org. Chem.* **1974**, *39*, 968−970. (b) Blunt, J. W.; Hartshorn, M. P.; Munro, M. H. G.; Soong, L. T.; Thompson, R. S.; Vaughan, J. *J. Chem. Soc., Chem. Commun.* **1980**, 820−821.

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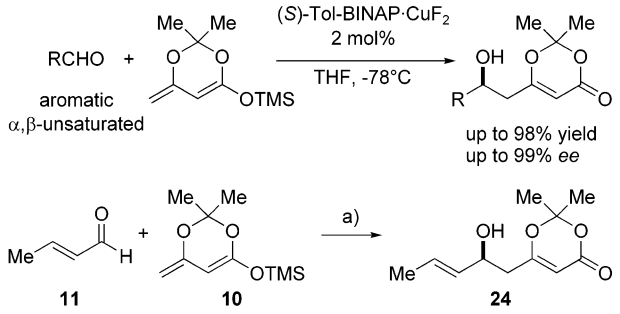
(36) Use of nBu$_4$NPh$_3$SiF$_2$ as anhydrous fluoride source has been reported and extensively used by DeShong. nBu$_4$NPh$_3$SiF$_2$ is conveniently prepared in two steps from triphenylsilanol, aqueous hydrofluoric acid, and nBu$_4$NF: (a) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166−5167. (b) Handy, C. J.; Lam, Y. F.; DeShong, P. *J. Org. Chem.* **2000**, *65*, 3542−3543.

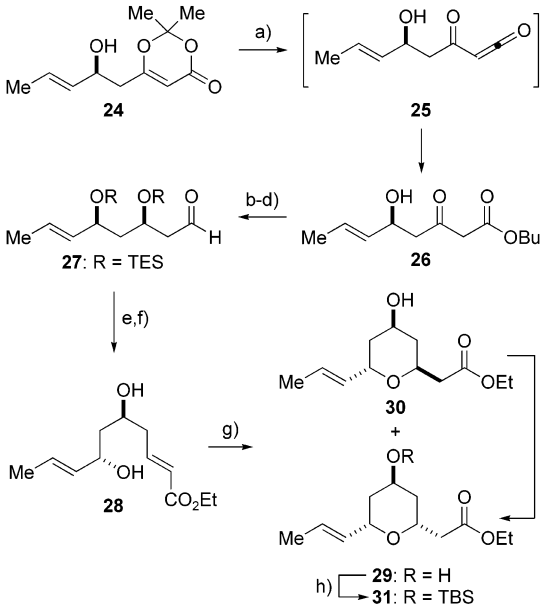
(37) Reaction was run on as much as 140 mmol of TMS-dienolate **10** without deterioration of the optical purity.

SCHEME 7[a]



[a] Reaction conditions: (a) (*R*)-Tol-BINAP (2.1 mol %), $Cu(OTf)_2$ (2.0 mol %), nBu$_4$NPh$_3$SiF$_2$ (4.0 mol %), THF, −78 °C, then **10** and **11**, 4 h, then TFA, 44%.

SCHEME 8[a]

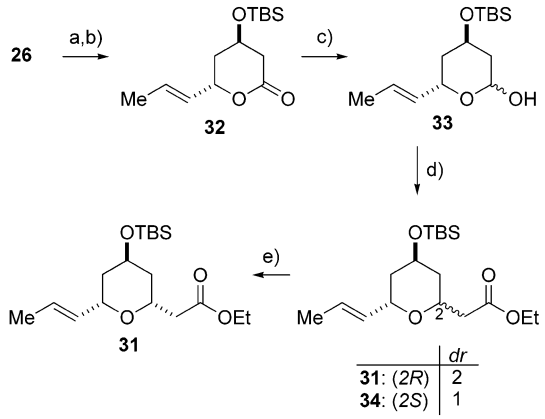


[a] Reaction conditions: (a) nBuOH, reflux, 1 h, 78%; (b) Et_3B, MeOH, THF, −78 °C, then **26** followed by $NaBH_4$, 5 h; (c) TESCl, imidazole, DMAP, DMF, rt, 12 h; (d) DIBAL-H, toluene, −78 °C, 30 min, 92% (over three steps) (dr > 95:5); (e) DBU, LiCl, $(EtO)_2P(O)CH_2CO_2Et$, CH_3CN, **27**, rt, 2 h; (f) nBu$_4$NF, THF, rt, 2 h, 80% (over two steps); (g) *t*BuOK (10 mol %), THF, 0 °C, 63% (dr = 10:1); (h) TBSCl, imidazole, DMAP, DMF, rt, 20 h, 96%;

In our earlier published approach,[17] conversion of keto ester **26** to the corresponding syn diol by stereoselective reduction using the method of Prasad ($NaBH_4$, Et_3B, MeOH, THF, −78 °C)[39] was followed by protection of the diol as bis-*O*-triethylsilyl ethers (TESCl, imidazole, DMAP, DMF) and semireduction of the butyl ester to aldehyde **27** with DIBAL-H in toluene (92% over three steps). Subsequent olefination with triethylphosphonoacetate under Roush−Masamune conditions[40] (DBU, LiCl, CH_3CN) and deprotection of the silyl ethers with nBu$_4$NF in THF led to diol **28** (80% over two steps). Treatment of diol **28** with catalytic amounts of *t*BuOK (10 mol %) in THF at 0 °C gave access to the desired 2,6-cis-disubstituted tetrahydropyran **29** in 63% yield and 10:1 diastereoselectivity.[41] The diastereomers could be easily separated by flash chromatography, and the undesired isomer **30** could be isomerized to **29** by resubmission to identical reaction conditions, showing that cyclization takes place under thermodynamic control. Protection of the secondary hydroxy group as a *tert*-butyldimethylsilyl ether (TBSCl, imidazole, DMAP, DMF) gave **31** (96%).

In a subsequent investigation en route to leucascandrolide A, we realized that the reaction sequence from **26** to **31** was rendered awkward by protective-group manipulations and needed further refinement and shortening. In the improved route, syn reduction of keto ester **26** was followed by acidic workup (PPTS, benzene). Protection of the secondary alcohol (TBSCl, imidazole, DMAP, rt, DMF) afforded lactone **32** in 77% yield (Scheme 9). Reduction of lactone **32** to the corresponding lactol **33** (DIBAL-H, toluene, −78 °C) and subsequent Horner−Wadsworth−Emmons reaction (triethylphosphonoacetate, NaH, THF, −78 °C) furnished a diastereomeric mixture of tetrahydropyrans **31** and **34** in 76% overall yield.[42] We were quite confident that we would be able to ensure diastereoselectivities similar to those previously obtained, given the fact that equilibration is possible under basic conditions (vide supra) and that A-values for hydroxy groups and the corresponding silyl ethers are nearly identical.[43] Upon treatment with catalytic amounts of *t*BuOK (10 mol %), the mixture cleanly equilibrated to the thermodynamically more stable isomer **31** (dr = 9:1). Not only is this modified reaction sequence two steps

SCHEME 9[a]



[a] Reaction conditions: (a) Et_3B, MeOH, THF, −78 °C, then **26** followed by $NaBH_4$, 5 h; then PPTS, PhH, reflux, 90 min; (b) TBSCl, imidazole, DMAP, DMF, rt, 2 h, 77% (over two steps); (c) DIBAL-H, toluene, −78 °C, 1 h; (d) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 °C → rt, 72% (over two steps); (e) *t*BuOK (10 mol %), THF, 0 °C, 4 h, 90% (dr = 9:1).

(38) Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431−2435.

(39) (a) Chen, K. M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923−1926. (b) Chen, K. M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155−158.

(40) (a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183−2186. (b) Eschenmoser first recognized that a tertiary amine and a lithium salt may be used instead of strong alkoxide or amide bases for the generation of enolates: Roth, M.; Dubs, P.; Gotschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710−734.

(41) Eliel, E. L.; Hargrave, K. D.; Pietrusiewicz, K. M.; Manoharan, M. *J. Am. Chem. Soc.* **1982**, *104*, 3635−3643. (b) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446−2453.

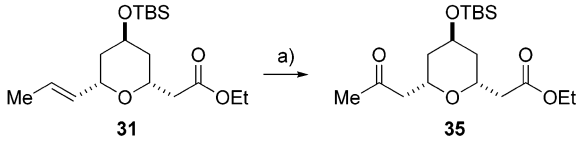
(42) Lactol **33** was formed as a mixture of diastereomers.

(43) Schneider, H. J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866−3873.

shorter than the initially reported route, but the overall yield from **26** to **31** is also improved (50% vs 44%).

Transformation of **31** to the desired methyl ketone **35** was intended to be carried out by Wacker oxidation (Scheme 10). Despite the great synthetic utility of this process, this reaction has found only limited application in the synthesis of complex molecules because of regioselectivity issues.[44] Indeed, oxidation of 1,2-disubstituted olefins generally leads to a mixture of isomeric ketones. However, good regioselectivity is often achieved in the oxidation of allylic or homoallylic ethers and esters,[45] although in the reported cases yields tend to be rather low (35−44%).[46] This enhanced regiocontrol has been speculated to be attributable to a nonsymmetrical bonding of palladium to the olefin as a consequence of coordination to the allylic or homoallylic oxygen.[46,47] When olefin **31** was treated with $PdCl_2$ (0.2 equiv), CuCl (1.2 equiv), and oxygen in a DMF/H_2O 7:1 mixture, methyl ketone **35** was obtained in good yield (86%) and complete regioselectivity. Although the reasons for this unusual result remain unclear, the Wacker process constitutes a good alternative to a two-step hydroboration/oxidation pathway. Thus, methyl ketone **35** was obtained in seven steps and 39% overall yield from known aldol adduct **24**.

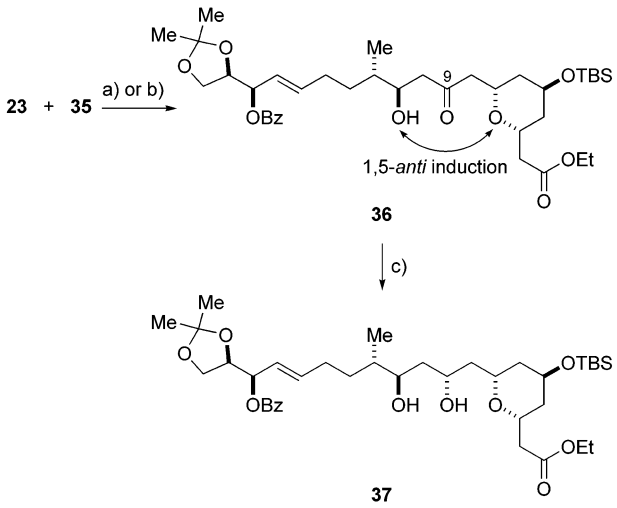
SCHEME 10[a]



[a] Reaction conditions: (a) $PdCl_2$ (20 mol %), CuCl (1.2 equiv), air, DMF/H_2O 7:1, rt, 48 h, 86%.

With multigram quantities of both key fragments **23** and **35** in hand, we next investigated their coupling by boron-mediated aldol addition (Scheme 11).[48] To this end, we examined the use of (−)-DIPCl (triple asymmetric induction) reported by Paterson[49] and Bu_2BOTf (double asymmetric induction) reported by Evans.[50] π-Facial selectivity of the diastereotopic carbonyl was imparted by the chiral aldehyde, the chiral ketone, and, in the case of (−)-DIPCl, the chiral boron reagent. Whereas the

SCHEME 11[a]



[a] Reaction conditions: (a) **35**, Bu_2BOTf, Et*i*Pr_2N, Et_2O, −78 °C, then **23**, 5 h, 80% (dr > 95:5); (b) **35**, (−)-DIPCl, Et_3N, Et_2O, −78 °C, then **23**, 24 h, 81% (dr > 95:5); (c) TABH, AcOH, CH_3CN, −40 °C, 70 h, 97% (dr > 95:5)

induction from the ketone and from the chiral boron reagent was expected to operate synergistically, stereoinduction from the aldehyde was expected to work in the opposite direction by Felkin−Anh[51] control. In both cases, the anti Felkin−Anh β-hydroxy ketone **36** was obtained in good yields (80% with Bu_2BOTf, 81% with (−)-DIPCl) as a single diastereomer, displaying the requisite 1,5-anti configuration found in the natural product.

Evans−Tishchenko reduction[52] of the C9 ketone in **36** would have been ideal, since the resulting 1,3-anti diol monoester **38** could have allowed for selective methylation of the C9 alcohol and thus full differentiation of all hydroxy groups (Scheme 12). Earlier studies in our laboratories had shown the feasibility of such an approach: model compound **39**, the C18 epimer of *ent*-**36**, was reliably reduced to **40** using acetaldehyde and catalytic amounts of SmI_2 (10−30 mol %) in excellent yields (>90%).[53] Ketone **36** proved to be resistant to these reaction conditions, and the desired product **38** was not formed. Instead, starting hydroxy ketone **36** was isolated, along with variable amounts of retro-aldol products. Recently, Scott has reported the use of $Sc(OTf)_3$ as a catalyst for stereoselective Tishchenko reduction of β-hydroxy ketones.[54] This protocol, when applied to **36**, did not lead to any improvement. Thwarted by the Tishchenko reduction, which was not without consequences for the subsequent steps, our synthetic planning needed some adjustment. As an alternative, reduction using tetramethylammonium triacetoxyborohydride cleanly afforded diol **37** in 97% yield and complete diastereoselectivity (>95:5 by ^1H NMR) (Scheme 11).[55] The presence

(44) No regioselectivity problems are generally encountered in the oxidation of terminal, monosubstituted olefins. Indeed, in this case, exclusive formation of the corresponding methyl ketones is generally observed. For an exception, see: Pellissier, H.; Michellys, P. Y.; Santelli, M. *Tetrahedron* **1997**, *53*, 7577−7586.

(45) (a) Tsuji, J.; Nagashima, H.; Hori, K. *Tetrahedron Lett.* **1982**, *23*, 2679−2682. (b) Lai, J. Y.; Shi, X. X.; Dai, L. X. *J. Org. Chem.* **1992**, *57*, 3485−3487.

(46) Wacker oxidation of a closely related tetrahydropyranyl-substituted olefin gave only one regioisomer, albeit in moderate yields of 35−44%. For details, see: Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474−3480.

(47) Pellissier, H.; Michellys, P. Y.; Santelli, M. *Tetrahedron* **1997**, *53*, 10733−10742.

(48) For an excellent review of asymmetric aldol reactions using boron enolates, see: Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1−200.

(49) (a) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581−8584. (b) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585−8588. (c) Paterson, I.; Collett, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187−1191.

(50) (a) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788−789. (b) The observation of double asymmetric induction using Cy_2BCl in related systems was first reported by Paterson: see ref 49 for details.

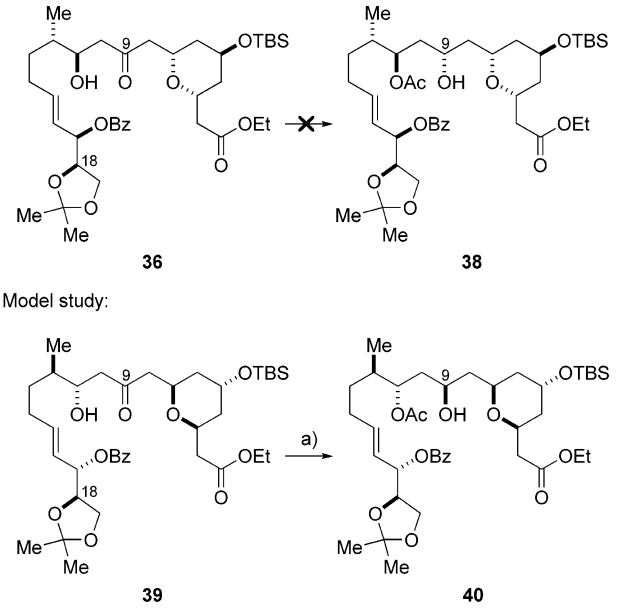
(51) Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, 155−158.

(52) (a) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449. (b) Tishchenko, V. *J. Russ. Phys. Chem. Soc.* **1906**, *38*, 355.

(53) THF (0.1 M) solutions of SmI_2 were freshly prepared from Sm and diiodoethane by standard procedures: (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693−2698. (b) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449.

(54) Gillespie, K. M.; Munslow, I. J.; Scott, P. *Tetrahedron Lett.* **1999**, *40*, 9371−9374.

SCHEME 12[a]



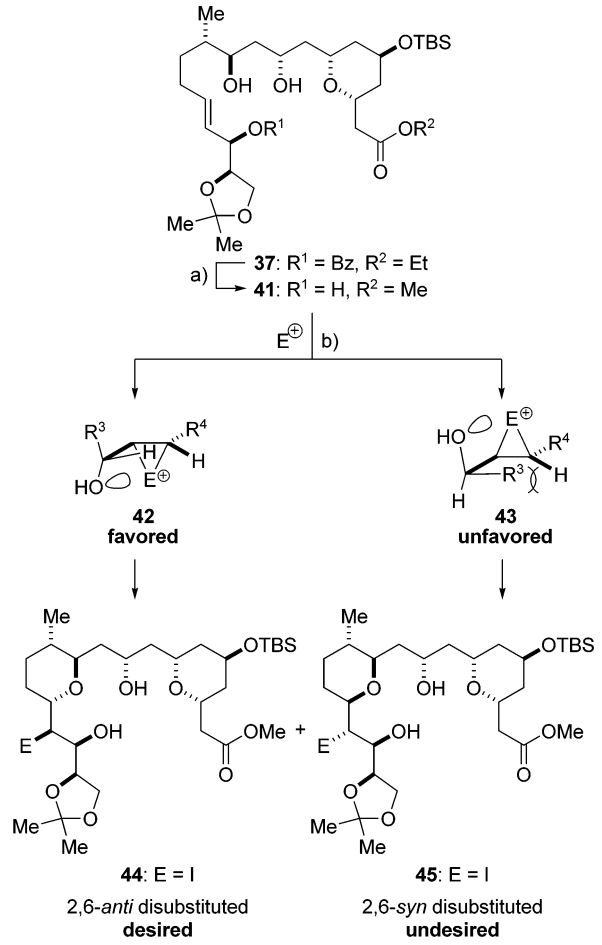
[a] Reaction conditions: (a) MeCHO, SmI_2 (10−30 mol %), THF, −78 °C, >85%.

of two secondary hydroxy groups left us with the problem of their differentiation, which we postponed to a later stage.

Deprotection of the allylic benzoate in **37** using K_2CO_3 in methanol with concomitant transesterification of the C1 ethyl ester afforded triol **41** in 92% yield (Scheme 11) and set the stage for one of the key steps of the leucascandrolide A synthesis: formation of the second tetrahydropyran ring by intramolecular electrophile-mediated cyclization onto a 6-hydroxy olefin (Scheme 13).[56] Although the related formation of tetrahydrofurans is well precedented, only a few examples leading to tetrahydropyrans have been reported. This ring closure was expected to lead selectively to the 2,6-trans-disubstituted tetrahydropyran by preferential formation of intermediate onium ion **42** as compared to **43** on the basis of previous studies by Chamberlin and Hehre.[57]

Iodine-based electrophiles (I_2 or IBr), however, showed little stereochemical preference, and a 1:1 diastereomeric mixture of easily separable **44** and **45** was obtained with I_2 and IBr.[58] Given that nucleophilic opening of the onium ion intermediates is a stereospecific process, the diastereochemical relationship between C16 and C17 (1,2-syn in **44** vs 1,2-anti in **45**) is correlated to the relative configuration of the newly installed stereocenter at C15. Upon treatment with K_2CO_3 in methanol, iodides **44** and

SCHEME 13[a]



[a] Reaction conditions: (a) K_2CO_3, MeOH, rt, 40 h, 92%; (b) IBr, 2,6-di-*tert*-butyl-4-methylpyridine, toluene, −78 °C, 2 h, 50% (dr = 1:1).

45 were converted to the corresponding epoxides **46** and **47**, respectively. Unambiguous stereochemical assignments of the relative configuration at C16 were made possible by comparison of the ^1H coupling constants of the vicinal epoxide protons (Scheme 14). Iodide **44** was shown to possess the requisite 2,6-trans-disubstituted tetrahydropyran ring, given the coupling constant of $^3J_{H-H} = 4.36$ Hz for **46**, characteristic for *cis*-epoxide. Epoxide **47** displays a coupling constant of $^3J_{H-H} = 2.16$ Hz, typical for *trans*-epoxide.

The use of selenium electrophiles led to a breakthrough in our efforts to optimize the diastereoselectivity. Phenylselenyl chloride gave a promising 75:25 selectivity of **48**/**49** (Scheme 15). Encouraged by this result, we turned our attention to bulkier, substituted arylselenyl reagents. In this respect, 2,4,6-triisopropylphenylselenyl bromide (TIPPSeBr) has been reported by Lipshutz to give improved selectivities in electrophile-mediated cyclizations of homoallylic alcohols to tetrahydrofurans[59] as compared to phenylselenyl chloride.[60] The use of this reagent gave the best results when applied to our system,

(55) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

(56) For reviews on electrophile-mediated cyclizations onto carbon−carbon multiple bonds, see: (a) Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 33−62. (b) Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 63−115.

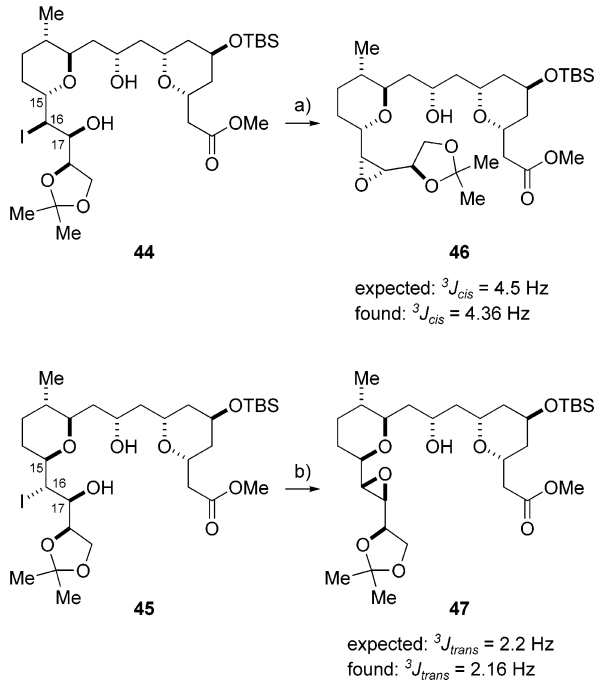
(57) (a) Chamberlin, A. R.; Mulholland, R. L. *Tetrahedron* **1984**, *40*, 2297−2302. (b) Chamberlin, A. R.; Mulholland, R. L.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672−677.

(58) Compared to I_2, IBr was shown to give enhanced diastereoselectivities at low temperatures in electrophilic cyclizations of homoallylic carbonates: (a) Duan, J. J.-W.; Smith, A. B., III. *J. Org. Chem.* **1993**, *58*, 3703−3711. (b) Duan, J. J.-W.; Sprengeler, P. A.; Smith, A. B., III. *Tetrahedron Lett.* **1992**, *33*, 6439−6442.

(59) Cyclizations of this type have been referred to as hybrid 6-*endo-tet*/5-*exo-tet* by Warren: McIntyre, S.; Warren, S. *Tetrahedron Lett.* **1990**, *31*, 3457−3460.

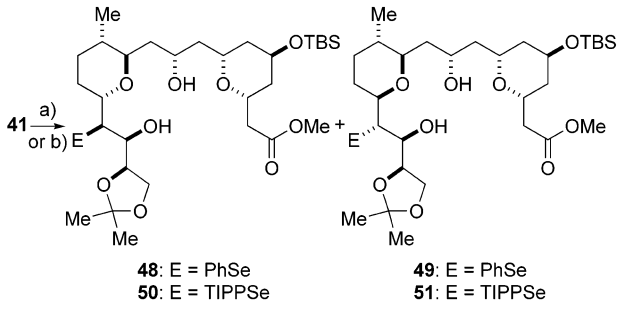
(60) Lipshutz, B. H.; Gross, T. *J. Org. Chem.* **1995**, *60*, 3572−3573.

SCHEME 14[a]



[a] Reaction conditions: (a) K_2CO_3, MeOH, rt, 15 h, 57%; (b) K_2CO_3, MeOH, rt, 15 h, 69%.

SCHEME 15[a]

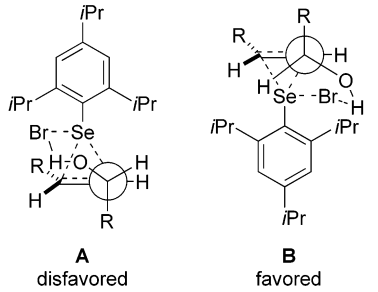


[a] Reaction conditions: (a) 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, −78 °C, followed by slow addition (over 1 h) of PhSeCl, 1 h, 78% (dr = 75:25 **48**/**49**); (b) 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, −78 °C, followed by slow addition (1 h) of **41**, 4 h, 74% (dr = 88:12 **50**/**51**).

leading to selenide **50** in 74% yield and a diastereomeric ratio of 88:12. Typical reaction procedures involve treatment of a solution of triol **41** and 2,6-di-*tert*-butyl-4-methylpyridine (5.0 equiv) in CH_2Cl_2 at −78 °C with a solution of the selenyl halide (4.0 equiv).[61]

To the best of our knowledge, the stereoselective formation of 2,6-trans-disubstituted tetrahydropyrans by intramolecular cyclization mediated by bulky selenium electrophiles is unprecedented. As a working model that accounts for the observed stereochemical outcome in the cyclization reaction, we propose that **B** represents the favored intermediate (Chart 1). The arrangement in **B** places the hydroxyl group in the outside position,[62] where it avoids destabilizing nonbonding interactions with the bulky aryl group.

CHART 1. Putative Arrangements for the Cyclization



In the earlier studies with IBr, we had observed that reductive deiodination of iodide **44** to **52** could be achieved in excellent yields (97%) using tributyltin hydride/AIBN in refluxing benzene (Scheme 16). However, purification and toxicity concerns associated with organotin reagents prompted us to investigate modern, alternative methods.[63] The silylated cyclohexadiene **53** recently reported by Studer could be used for tin-free radical reduction, providing **52** in an operationally much simpler way that did not require the use of deoxygenated solvents.[64] Mechanistically, the reduction is suggested to proceed via a cyclohexadienyl radical, which undergoes aromatization with concomitant generation of a *tert*-butyldimethylsilyl radical able to propagate the chain reaction. Thus, upon treatment with **53** and AIBN in refluxing hexane, iodide **44** afforded **52** in 85% yield, whereas selenide **50** was converted to **52** in 80% yield.

In preparation for the subsequent macrocyclization reaction, hydrolysis of **52** using TMSOK (Scheme 18) afforded seco acid **56**, which was used without further purification. It is worth noting that initial attempts using LiOH or NaOH proved to be low-yielding.

The failure of the Tishchenko reduction at an earlier point in the synthesis (vide supra) still left unresolved a hydroxy group differentiation problem (at C9 and C17). At this point, we planned to examine whether selective macrolactonization would lead to differentiation. Although formation of the eight-membered lactone **59** is conceivable,[65] we expected the thermodynamic bias to be considerably in favor of the larger macrocycle **57**.[66] In an earlier model study, macrolactonization of **54**,[67] the C18 epimer of *ent*-**56**, was achieved in 80% yield employing the Yamaguchi protocol[68] (formation of the mixed anhydride by treatment with 2,4,6-$C1_3(C_6H_2)$COCl/Et_3N, followed by DMAP-promoted cyclization) (Scheme 17).[69]

(61) (a) The relative configuration of **50** could be assigned only after reductive removal of the phenylselenyl moiety by comparison with **52** obtained from iodide **44**. (b) In the absence of 2,6-di-*tert*-butyl-4-methylpyridine, deprotection of the C5 silyl ether was observed.

(62) (a) Houk, K. N.; Moses, S. R.; Wu, Y. D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880−3882. (b) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951−3954.

(63) For a review on tin-hydride substitutes in reductive radical chain reactions, see: Studer, A.; Amrein, S. *Synthesis* **2002**, 835−849.

(64) Studer, A.; Amrein, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3080−3082.

(65) Harrison, J. R.; Holmes, A. B.; Collins, I. *Synlett* **1999**, 972−974.

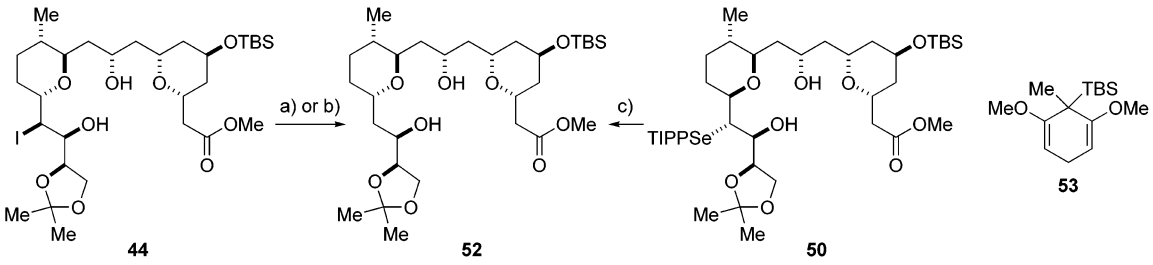
(66) For a general discussion on the energetics of lactonization, see: Mandolini, L. *J. Am. Chem. Soc.* **1978**, *100*, 550−554.

(67) Seco acid **54** was prepared from **40** by O-methylation of the C9 hydroxy group, followed by a reaction pathway similar to that described for the conversion of diol **37** to seco acid **56**.

(68) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

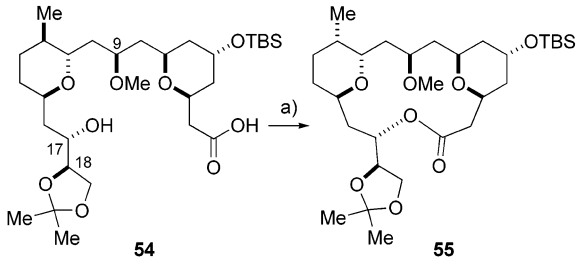
(69) Leighton and Rychnovsky have reported similar Yamaguchi macrolactonization reactions with substrates incorporating a C9 methyl ether, giving macrocycles in good yields. See ref 8 and 9.

SCHEME 16[a]



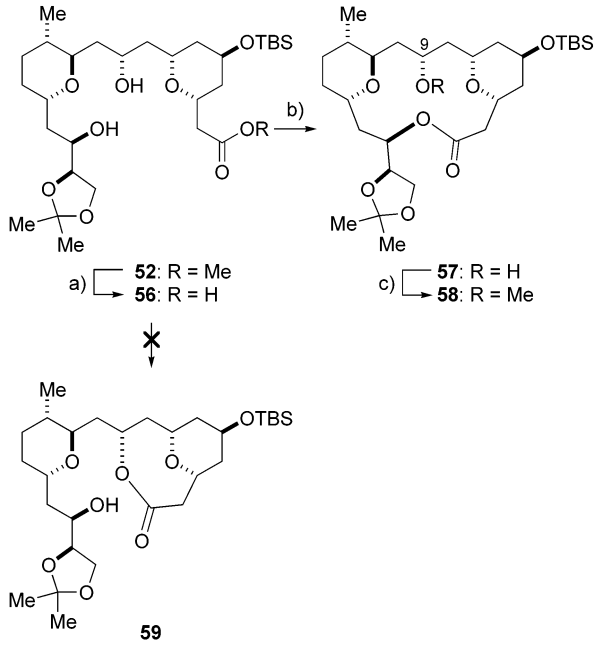
[a] Reaction conditions: (a) nBu$_3$SnH, AIBN, PhH, reflux, 1 h, 97%; (b) **53**, AIBN, hexane, reflux, 2 h, 85%; (c) **53**, AIBN, hexane, reflux, 2 h, 80%.

SCHEME 17[a]



[a] Reaction conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et$_3$N, THF, rt, 1 h; then addition to DMAP in THF, 80%.

SCHEME 18[a]



[a] Reaction conditions: (a) TMSOK, Et$_2$O, rt, 24 h; (b) 2,4,6-trichlorobenzoyl chloride, Et$_3$N, rt, 1 h, then dilution with DMF and slow addition (3 h) to DMAP in DMF, rt, 2 h; (c) Me$_3$OBF$_4$, Proton Sponge, 4 Å MS, rt, 30 min, 49% (over three steps).

By contrast, **56** proved to be recalcitrant to cyclization when submitted to otherwise identical conditions, and no trace of **57** could be isolated. Various solvents typically used in this type of reaction were screened (benzene, toluene, xylene, THF). However, these studies were frustrated by the unexpected inertness of **56** toward cyclization, leading to the exclusive formation of oligomeric products despite slow addition (up to 24 h) and high dilution (10^{-3} M).

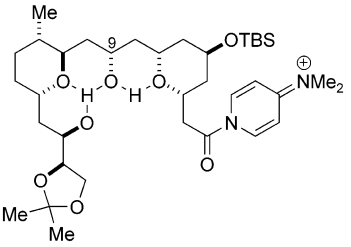


FIGURE 3. Postulated hydrogen-bonded array.

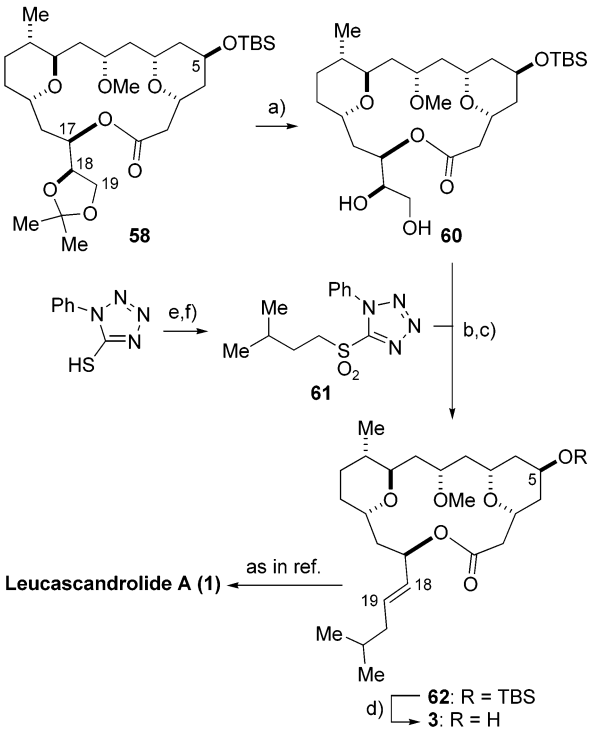
The difference in reactivity between acids **54** and **56** could be ascribed to various factors. Indeed, subtle stereochemical modifications have been shown to critically influence macrocyclization reactions and impact their success or failure.[70] We hypothesized that the difference in reactivity was attributable to the presence of a network of hydrogen bonds in **56** that is absent in **54**. This network leads to an arrangement that may lock the molecule in a conformation that is unfavorable for ring closure. Molecular-mechanics calculation reveals that in the preferred conformation of the macrocyclic structure, the C9 methyl ether resides peripherally, a disposition that is not compatible with the postulated hydrogen-bonded array, where the C9 hydroxy group supposedly resides between the tetrahydropyran rings (Figure 3).[5]

This hypothesis could be tested. As such, we attempted the cyclization reaction in a polar solvent able to disrupt hydrogen bonds. Indeed, the use of DMF led to the formation of the desired macrocycle **57** upon addition of the intermediate mixed anhydride to a solution of DMAP. The protocol used involves addition of the mixed anhydride (2.4×10^{-3} M in THF/DMF) to a solution of DMAP (10 equiv; 1.5×10^{-2} M in DMF) over 3 h (Scheme 18).[71]

(70) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Auyeung, B. W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chenevert, R. B.; Fliri, A.; Frobel, K.; Gais, H. J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Babu, T. V. R.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N. C. *J. Am. Chem. Soc.* **1981**, *103*, 3213−3215.

(71) We were worried that the increased polarity of the solvent may lead to epimerization at C3 by retro-Michael/Michael reaction. However, no scrambling of this stereogenic center was observed as judged by ^{1}H NMR.

SCHEME 19[a]



[a] Reaction conditions: (a) AcOH/THF/H_2O 2:1:1, 45 °C, 5 h, 80%; (b) $Pb(OAc)_4$, EtOAc, 0 °C, 15 min; (c) **61**, KHMDS, DME, −78 °C → −55 °C, 2 h; 73% (over two steps); (d) *n*Bu_4NF, THF, 0 °C → rt, 7 h, 98%; (e) PPh_3, DEAD, THF, rt, 16 h, 86%; (f) Oxone, MeOH, H_2O, rt → 50 °C, 21 h, 90%.

No trace of the eight-membered macrocycle **59** could be detected by ^{1}H NMR.

O-Methylation of the C9 alcohol was conveniently achieved with Me_3OBF_4 in combination with proton sponge and 4 Å molecular sieves to give **58** in 49% yield from methyl ester **52**.[72]

Unmasking of the C18, C19 diol was achieved in 80% yield by careful hydrolysis of the isopropylidene ketal in **58** under mild acidic conditions by heating to 45 °C in AcOH/THF/H_2O 2:1:1,[73] leaving the C5−OTBS group undisturbed (Scheme 19). Subsequent cleavage ($Pb(OAc)_4$, EtOAc, 0 °C) of the resulting 1,2-diol **60** resulted in the formation of an aldehyde, which was used without further purification and taken immediately to the next step. The C17 side chain was introduced using the one-pot Kocieński[74] modification of the Julia−Lythgoe olefination[75] with sulfone **61**.[76] This approach, particularly alluring since the reaction leads to high (*E*)-selectivities in the absence of α-branching or conjugation, involved treatment of sulfone **61** with KHMDS in DME as a solvent, followed by addition of the aldehyde and warming to ambient temperature. The desired disubstituted olefin **62** was formed as the sole geometric isomer in 73% yield over two steps. No trace of the (*Z*)-isomer could be detected by ^{1}H NMR analysis.

Completion of the formal synthesis required, as the final step, the cleavage of the C5 *tert*-butyldimethylsilyl ether. Deprotection of **62** with excess *n*Bu_4NF in THF proceeded smoothly and provided the leucascandrolide A macrolide **3** in 98% yield. This synthetic material proved to be identical in all respects (^{1}H NMR, ^{13}C NMR, $[\alpha]_D$, IR, HRMS) to the material obtained by degradation from the natural product[5] and to the material previously synthesized by Leighton[8] and Rychnovsky.[9] With **3** in hand, we completed the total synthesis of leucascandrolide A, which could be achieved by the two-step sequence involving esterification and Still−Gennari modification of the Wittig olefination as previously reported by Leighton, giving fully synthetic leucascandrolide A.[5,8]

Conclusion

The structure of leucascandrolide A, its biological profile, and its lack of availability conspire to make this natural product an important target for chemical synthesis. We have described a synthesis route that effectively provides access to the macrolide core in 19 steps and, following attachment of the C5 side chain, to the natural product in an additional two steps. The salient features of the route include: the use of a selenium-mediated cyclization affording a 2,6-trans-substituted tetrahydropyran and the application of modern methods for asymmetric C−C bond formation such as alkynyl-zinc addition to (*R*)-isopropylidene glyceraldehyde and an enantioselective dienolate aldol addition reaction to crotonaldehyde. The full account of the work described herein provides a detailed discussion of the investigations conducted in the course of implementing these new methods; additionally, we document unexpected observations pertaining to an unwieldy reduction of a hydroxyl ketone intermediate and the influence of putative hydrogen-bonding effects on macrolactonization. Moreover, we delineate a synthesis of the key C1−C10 methyl ketone intermediate that is considerably improved over the approach we initially reported. Given the intense research activity on this marine natural product, the investigations we have detailed should find relevance in ongoing research of its chemistry and biology.

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Supporting Information Available: Experimental procedures and spectral data for all relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(76) Sulfone **61** was prepared from 3-methyl-1-butanol and commercially available 1-phenyl-5-mercaptotetrazole using the Mitsunobu protocol (86%) followed by oxidation of the resulting sulfide to the corresponding sulfone **61** with oxone in 90% yield.