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Leucascandrolide A: A Second Generation Formal Synthesis

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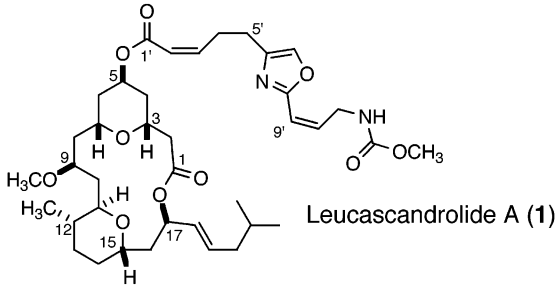
ABSTRACT



A convergent, second generation formal synthesis of (+)-Leucascandrolide A (1) has been efficiently achieved by providing a flexible, enantiocontrolled strategy toward the bioactive macrolactone component. Advancements for stereocontrol in asymmetric allylation methodology are discussed. Efforts feature novel results for reductions using the Terashima hydride reagent.

Leucascandrolide A (**1**) was isolated by Pietra and coworkers from *Leucascandra caveolata*, a calcareous sponge first found in 1989 along the eastern coast of New Caledonia in the Coral Sea.[1] Detailed structural analysis revealed a pattern of extensive 1,3-oxygenation in an 18−membered macrolactone that was bridged by ether oxygens forming two internal pyrans.[1] An unusual side chain bearing two *Z*-olefins, an oxazole, and a terminal carbamate was attached to the C_5 hydroxyl of the macrolide via an ester linkage. Assays of leucascandrolide A displayed strong in vitro anticancer properties with IC_{50} values of 0.05 and 0.25 μg/mL against KB tumor and P338 murine leukemia cell lines, respectively.[1] Significantly, strong inhibition was also found against *Candida albicans*, a pathogenic yeast that infects HIV patients, presaging the progression to AIDS.[1] The macrolactone portion of **1** was later shown to be essential for cytotoxic activity, while the oxazole-containing side chain contributed to the antifungal properties of the natural product. This promising bioactivity necessitated further biological evaluations. However, samples subsequently harvested in 1994 at a location north of the previous sampling area failed to yield a trace of leucascandrolide A. Pietra has suggested that **1**, as well as leucascandrolide B,[2] may have origins in an opportunistic microbial colonization of extensively dead portions of the sponge isolated in the earlier sampling. These facts have prompted numerous efforts toward the synthesis of **1**, which have led to successful pathways for the preparation of racemic and optically active natural product.[3] Herein we report an enantiocontrolled second generation pathway to the macrolactone of **1** that is readily amenable to the production of analogues for structure−activity investigations.

Our previous synthesis of leucascandrolide A (**1**) demonstrated the application of reagent-based asymmetric allyla-

(1) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51.

(2) D'Ambrosio, M.; Tatò, M.; Pocsfalvi, G.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 347.

(3) (a) Crimmins, M. T.; Siliphaivanh, P. *Org. Lett.* **2003**, ASAP Article. (b) Williams, D. R.; Plummer, S. V.; Patnaik, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3934. (c) Paterson, I.; Tudge, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 343. Paterson, I.; Tudge, M. *Tetrahedron* **2003**, *59*, 6833. (d) Fettes, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4098. Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, ASAP Article. (e) Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670. (f) Wipf, P.; Reeves, J. T. *Chem. Commun.* **2002**, 2066. (g) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420. (h) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894.

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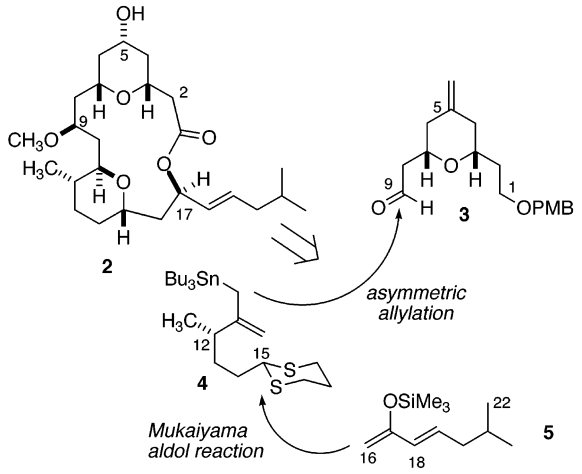
tion[4] to provide a highly convergent and stereocontrolled construction of the natural product.[3b] During the course of our studies, Kozmin and co-workers reported a facile Mitsunobu displacement reaction for convenient attachment of the intact ester side chain at C_5 of racemic **1**.[3e] Thus the efficient enantiocontrolled preparation of macrolactone **2** could provide for the systematic inclusion of a variety of C_5 ester substituents.

As summarized in Scheme 1, we envisioned the assembly

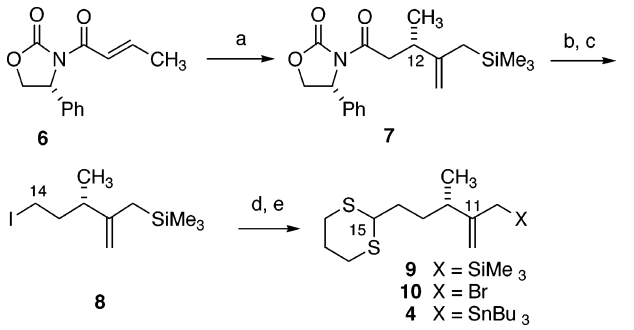
Scheme 1



of macrolide **2** via three readily available components of modest complexity, which evoked further enthusiasm for these studies. Moreover, our previous efforts had provided substantial quantities of the optically pure tetrahydropyran **3** (C_1-C_9). To that end, we considered the use of stannane **4** in asymmetric allylation methodology for reagent-based control of stereochemistry at C_9 of **2**. The subsequent formation of the $C_{15}-C_{16}$ carbon bond via a modified Mukaiyama aldol strategy would utilize the silylenol ether **5**. Remaining issues to be addressed involved stereocontrol in the generation of the 2,6-*trans*-tetrahydropyran and in the formation of the equatorial alcohol at C_5 of **2**.

The application of asymmetric conjugate addition methodology, as reported from these laboratories,[5] facilitated a five-step preparation of the nonracemic allylic stannane **4** (Scheme 2). Diastereoselective 1,4-addition of the organocopper species derived from the Grignard reagent of 2-bromoallyltrimethylsilane with the (*R*)-4-phenyl-*N*-enoyl-1,3-oxazolidin-2-one **6** gave imide **7** (dr > 20:1), installing the C_{12} chirality.[6] After reductive cleavage of the chiral auxiliary with $LiBH_4$, the resultant pure alcohol was directly trans-

Scheme 2[a]



[a] (a) $CH_2{=}C(Br)CH_2SiMe_3$, Mg^0, then CuBr·DMS, THF, −40 °C, then **6**, −78 to −20 °C, 75% (>95% dr); (b) $LiBH_4$, MeOH, Et_2O, 0 °C, 81%; (c) DCC·MeI, THF, 88%; (d) 2-lithiodithiane, THF, −78 to 0 °C, 96%; (e) NBS, propylene oxide, −78 °C, CH_2Cl_2/DMF (3:4), then add Bu_3SnLi, CuBr·DMS to crude allyl bromide, −78 to −40 °C, 70−80% overall from **9**.

formed into primary iodide **8** in 88% yield using dicyclohexylcarbodiimide and methyl iodide.[7] A number of standard procedures for this conversion were not compatible with the allylic silane. Low-temperature alkylation with 2-lithio-1,3-dithiane led to **9**, and treatment with recrystallized *N*-bromosuccinimide at −78 °C in a solution of DMF and CH_2Cl_2 gave the intermediate allyl bromide **10**. This transformation is especially notable because NBS is routinely used to promote the cleavage and hydrolysis of dithioacetals. Additionally, the decomposition of the reactive allylic bromide via S-alkylation must be avoided. Thus, the crude bromide was used directly for displacement with tri-*n*-butylstannyl copper[8] to provide the $C_{10}-C_{15}$ component **4**.

The transmetalation of stannane **4** (Scheme 3) with (4*R*,5*R*)-2-bromo-4,5-diphenyl-1,3,2-diazoborolidine **11**[9] was followed by the low-temperature condensation with aldehyde **3** to provide a quantitative yield of the homoallylic alcohol **12** along with small amounts of the corresponding (9*S*)-alcohol diastereomer (dr 91:9). The stereochemistry at C_9 of **12** was confirmed with NMR analysis of its Mosher esters;[10] however, on a preparative scale, this mixture was carried forward for two steps.

A predictive model of our rationalization for this asymmetric allylation is illustrated in Figure 1. Thus, the allylic transposition of **4** to the reactive borane **13** is followed by synclinal complexation of the Lewis acid with respect to the aldehydic hydrogen in **14**. This preorganization is depicted by the chairlike arrangements **15** and **16**. Simple diastereoselection, as determined by the (*R*,*R*)-auxiliary, is based upon the unfavorable nonbonded interactions of the sulfonyl

(4) For additional examples: (a) Williams, D. R.; Brooks, D. A.; Meyer, K. G.; Clark, M. P. *Tetrahedron Lett.* **1998**, *39*, 7251. (b) Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924. (c) Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765.

(5) (a) Williams, D. R.; Kissel, W. S.; Li, J. J. *Tetrahedron Lett.* **1998**, *39*, 8593. (b) Williams, D. R.; Kissel, W. S.; Li, J. J., Mullins, R. J. *Tetrahedron Lett.* **2002**, *43*, 3723. (c) Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766.

(6) The stereochemistry of **7** was assigned by protodesilyation and comparison with known material (see ref 5a).

(7) Scheffold, R.; Saladin, E. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 229. For a recent application, see: Harmata, M.; Bohnert, G. J. *Org. Lett.* **2003**, *5*, 59.

(8) Piers, E.; Chong, J. M.; Gustafson, K.; Andersen, R. J. *Can. J. Chem.* **1984**, *62*, 1.

(9) Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495.

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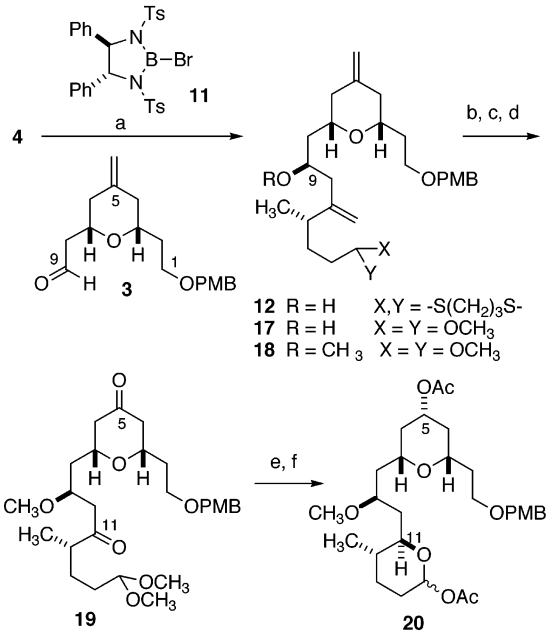
Scheme 3[a]



[a] (a) (*R*,*R*)-**11**, CH_2Cl_2, **4**, rt, 10 h then −78 °C, **3**, 2 h, quant, dr 91:9; (b) $PhI(OOCCF_3)_2$, MeOH, 77%; (c) Me_3OBF_4, proton sponge, 4 Å MS, CH_2Cl_2, 97%; (d) OsO_4, NMO, acetone, H_2O, then $NaIO_4$, THF/H_2O (1:1), 90%; (e) excess $LiAlH_4$/(+)-*N*-methylephedrine/*N*-ethylaniline (1:1:2), Et_2O, −78 °C, 96%; (f) H_3PO_4, THF/H_2O(3:2), then add Ac_2O, py., DMAP, CH_2Cl_2 to crude lactol, 85%.

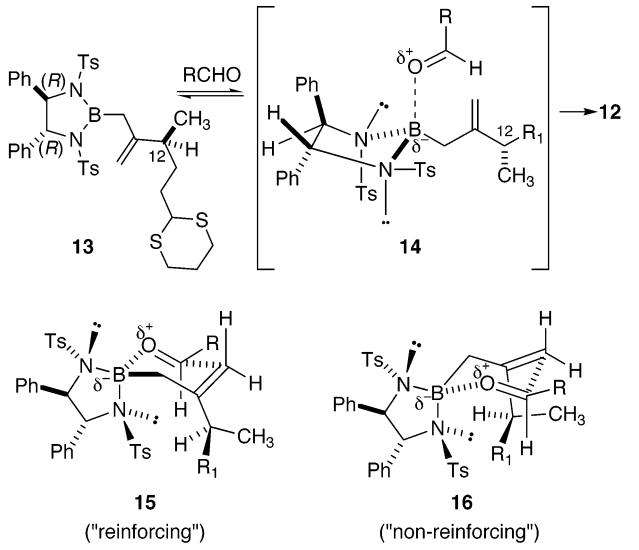


Figure 1. Diasteroselection in allylation reactions.

substituent and aldehyde in **16**.[11] Therefore, this C_2-symmetric (*R*,*R*)-controller generally favors *re*-face addition as shown in **15**. The introduction of steric interactions as a result of allylic branching in the starting stannane **4** (at C_{12}) provide additional complexity.[12] As illustrated in **16**, attempts to minimize A(1,3) strain in the allyl borane will project methyl or R_1 into the chairlike transition state and serves to destabilize this situation. On the other hand, the reinforcing scenario in **15** permits a minimization of A(1,3) interactions[13] and directs the C_{12} methine into the region of the sulfonyl group of the auxiliary. Our rationale is supported by parallel experiments using the corresponding (*S*,*S*)-borane of **11**, which led to a mismatched condensation favoring the (9*S*)-diastereomer of **12** in a modest 2:1 ratio. Stereogenicity in the aldehyde component **3** (at β-carbon C_7) plays a less significant role in the outcome of these allylations.[14]

Upon exchange of the dithiane for the dimethyl acetal under Stork conditions,[15] the C_9 secondary alcohol underwent quantitative methylation. Flash silica gel chromatography at this point conveniently separated the minor C_9 diastereomer from the previous allylation, yielding pure **18**. Subsequent oxidative cleavage of the C_5 and C_{11} olefins furnished diketone **19**, which was subjected to the Terashima reduction via the in situ generation of a $LiAlH_4$ complex of (+)-*N*-methylephedrine and *N*-ethylaniline.[16] This unprecedented utilization of the Terashima reagent effected a highly selective Felkin−Anh addition to provide the (11*R*)-alcohol (dr > 25:1) and also reduced the more accessible C_5 ketone with axial hydride delivery to yield the equatorial hydroxy group (dr 8:1) in the product diol. Sequential exposure to aqueous protic acid and then acetic anhydride and pyridine gave the diacetate **20**.

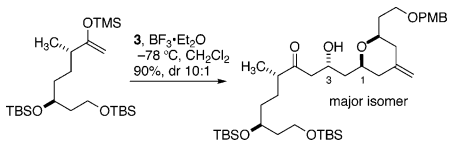
The stage was set for the incorporation of the C_{16}−C_{22} component via a Mukaiyama aldol process. Thus, Lewis acid catalysis provided for a diastereofacial condensation of TMS enol ether **5** with **20** to directly install the *E*-unsaturated ketone of **21** (dr > 25:1) in excellent yield (90%). Selective formation of the *trans*-tetrahydropyran in **21** was anticipated by axial nucleophilic addition to the intermediate oxocarbenium.[17] During the course of our investigations, Paterson and co-workers described similar findings.[3c]

(11) Our molecular modelling indicates nonbonded interactions of the axially disposed aldehydic H and the sulfonyl oxygens in **16**.

(12) Stereogenecity in the starting stannane, which positions a chiral center at the β-carbon of the C-2 appendage with respect to the allyl nucleophile (or is more remote), does not affect the diastereofacial selectivity imposed by the auxiliary. For a full account of this work, see: Williams, D. R.; Meyer, K. G.; Shamim, K.; Patnaik, S. *Can. J. Chem.* In press.

(13) The energy requirements for the A(1,3) strain are estimated to be in the range of 0.4−0.7 kcal/mol for the CH_3/H interaction: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(14) The addition of TMS enol ethers to substrates such as **3** proceed with a high level of 1,3-*anti* stereocontrol via open transition states. For a discussion, see: Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322. Similar trends were observed in our C_9−C_{10} coupling studies, as exemplified by the following reaction:

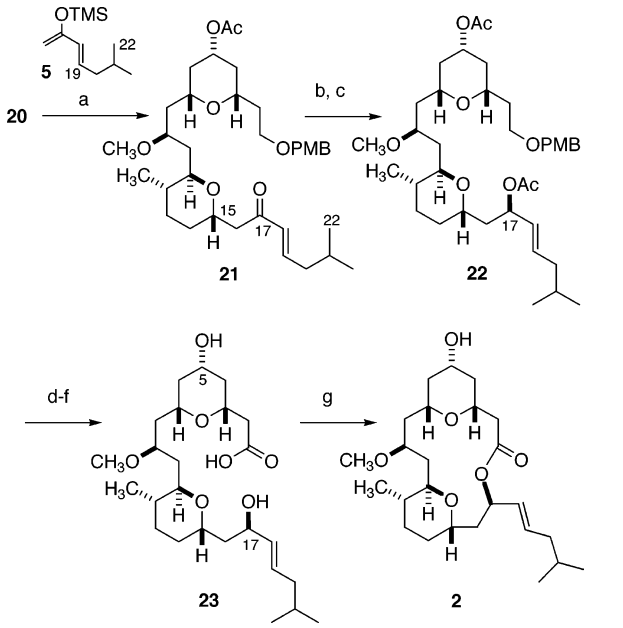


(15) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.

(16) (a) Terashima, S.; Tanno, N.; Koga, K. *J. Chem. Soc., Chem Commun.* **1980**, 1026. (b) Terashima, S.; Tanno, N.; Koga, K. *Chem Lett.* **1980**, 981. (c) Tanno, N.; Terashima, S. *Chem. Pharm. Bull.* **1983**, *31*, 837.

(17) This stereochemical outcome is anticipated. For recent examples from these laboratories, see: (a) Williams, D. R.; Mi, L.; Mullins, R. J.; Stites, R. E. *Tetrahedron Lett.* **2002**, *43*, 4841. (b) Williams, D. R.; Heiderbrecht, R. W., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 1843.

Scheme 4[a]



[a] (a) **20**, $ZnCl_2$, (1 M in Et_2O), CH_2Cl_2, −78 °C to rt, 90%, dr >25:1; (b) *S*-Me-oxazaborolidine, BH_3·THF, THF, −10 °C, 85%, dr 5:1; (c) Ac_2O, pyr, DMAP, CH_2Cl_2, 95%; (d) DDQ, CH_2Cl_2, pH 7 buffer, ^{t}BuOH, 96%; (e) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2 then $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, aq ^{t}BuOH, 0 °C; (f) NaOMe MeOH, (98% over 3 steps); (g) 2,4,6-trichlorobenzoyl chloride, THF, Et_3N, slow addition to refluxing solution of DMAP in PhH, 60%.

Final stages for the synthesis proceeded uneventfully. The Corey CBS borohydride reduction[18] of **21** using (*S*)-2-methyl-oxazaborolidine gave a 5:1 mixture of separable C_{17} alcohols favoring the (17*R*)-isomer.[19] Unfortunately chirally modified Terashima[16] or Noyori[20] reagents commonly deployed for reduction of aromatic and acetylenic ketones and enones led to significant (>50%) 1,4-conjugate hydride reduction. Following acetylation to **22** and DDQ deprotection, sequential oxidations under Dess−Martin[21] and Pinnick[22] conditions led to the C_1 carboxylic acid, which was stirred with sodium methoxide to produce the *seco*-acid **23** (98% yield over three steps). On a preparative scale, flash silica gel chromatography of the pure *seco*-acid permitted the convenient separation of the minor (17*S*)-diastereomer to give pure **23**. Yamaguchi macrolactonization[23] led to the formation of the 18-membered **2** (60%),[24] which proved to be identical in all respects with reported spectroscopic and physical data for this substance as described by the isolation and characterization studies of Pietra and co-workers.[1,25]

In summary, a convergent enantiocontrolled pathway to the macrolide core of leucascandrolide A has been achieved in 21 steps (7% overall yield) from readily available starting substances. The reagent-controlled nature of this synthesis allows the flexibility required for analogue syntheses. Our asymmetric allylation methodology highlights the role of vicinal stereochemistry in the stannane component for reinforcing interactions with the chiral auxiliary. The use of the Terashima reduction demonstrates a powerful technique for the stereocontrolled generation of 1,3-polyol derivatives.

Acknowledgment. The authors gratefully acknowledge the National Institute of Health (GM-42897) for the generous support of our work.

Supporting Information Available: Experimental procedures and spectral data for compounds **2**, **4**, **7**−**9**, **12**, and **17**−**23** on the synthesis pathway are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) The stereochemistry of the major (17*R*)-diastereomer was confirmed by modified Mosher ester analysis (see ref 10).

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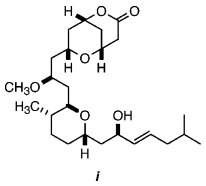
(24) Yamaguchi conditions also led to small amounts (5−15%) of the [3.3.1]-bicyclic lactone *i*, which can be recycled to the *seco*-acid **23** via KOH, aqueous methanol.



i

(25) In addition, macrolide **2** underwent oxidation to the corresponding C_5 tetrahydropyranone; for direct comparison with a sample independently prepared from our first generation strategy, see ref 3b.