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Efficient Stereochemical Relay en Route to Leucascandrolide A

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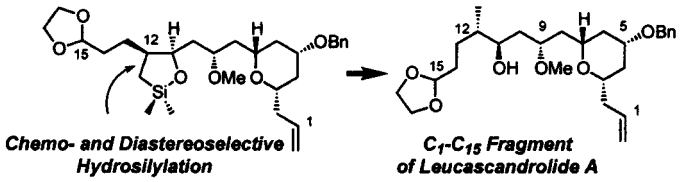
ABSTRACT



A complete relay of the initial stereochemical information is central to the efficient and highly stereocontrolled construction of the C_1–C_{15} fragment of the marine macrolide leucascandrolide A. Cyclic silane 3, assembled via Pt-catalyzed hydrosilylation, was designed to serve as a temporary template for the installation of the C_{12} stereogenic center. The strategy features a highly convergent C_{10}–C_{11} bond construction via 1,5-*anti*-selective aldol reaction and rapid assembly of the trisubstituted pyran subunit via Prins desymmetrization.

Efficient assembly of diverse stereochemical arrays containing multiple stereogenic centers plays a pivotal role in target-oriented synthesis. Advances in asymmetric synthesis involving the use of external chiral controllers (i.e., auxiliaries, reagents or catalysts) have simplified solutions of many challenging stereochemical puzzles.[1] However, creation of new chiral elements by means of internal asymmetric induction utilizing substrate-based diastereochemical relay often represents a more direct and efficient approach.[2] The ideal scenario entails formation of all asymmetric centers of the target compound starting from a single stereogenic point without any additional external chirality being used in the assembly process.[2d]

Aiming at the development of an efficient and practical strategy featuring a complete acyclic stereochemical relay, we recently initiated a program aimed at the synthesis of leucascandrolide A (**1**), a highly bioactive marine macrolide isolated by Pietra et al. from a new genus of calcareous sponges, *Leucascandra caveolata* (Scheme 1).[3,4] Due to the difficulty in isolating leucascandrolide A, combined with the presently unknown biogenetic origin,[5] an efficient chemical synthesis of this macrolide would provide an ideal approach for its efficient production for further pharmacological evaluation.[6] Herein, I present a convergent, highly stereocontrolled assembly of the C_1-C_{15} fragment (**2**) representing the central portion of leucascandrolide A and incorporating six of the requisite stereogenic centers.

Retrosynthetically, subtarget **2** was envisioned to derive from hydroxy ketone **4** via a series of diastereo- and chemoselective transformations involving reduction of the

(1) (a) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984. (b) Ager, D. J.; East, M. B. *Asymmetric Synthetic Methodology*; CRC Press: Boca Raton, 1996. (c) Hayashi, T.; Tomioka, K.; Yonemitsu, O. *Asymmetric Synthesis*; Kodansha: Tokyo, 1998.

(2) (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3−72. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370. (c) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223. (d) Smith, A. B., III; Empfield, J. R. *Chem. Pharm. Bull.* **1999**, *47*, 1671−1678.

(3) (a) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51−60. (b) For isolation of leucascandrolide B, see: D'Ambrosio, M.; Tatò, M.; Pocsfalvi, G.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 347−353.

(4) For a recent total synthesis of leucascandrolide A, see: (a) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894−12895. For another synthetic approach, see: (b) Crimmins, M. T.; Carroll, C. A.; King, B. W. *Org. Lett.* **2000**, *2*, 597−599. (c) Vakalopoulos, A.; Hoffmann, H. M. R. *Org. Lett.* **2001**, *3*, 177−180.

(5) Several lines of evidence presently suggest that leucascandrolide A may originate from the microbial organism present in *L. caveolata*.

(6) In preliminary in vitro studies, leucascandrolide A displayed potent cytotoxicity against KB and P388 tumor cell lines (IC_{50} 50 ng/mL and 0.25 μg/mL respectively), as well as strong inhibition of *Candida albicans*.

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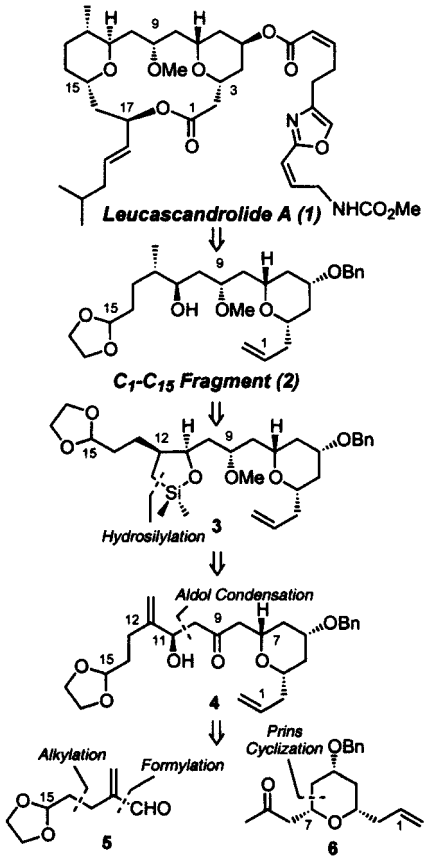
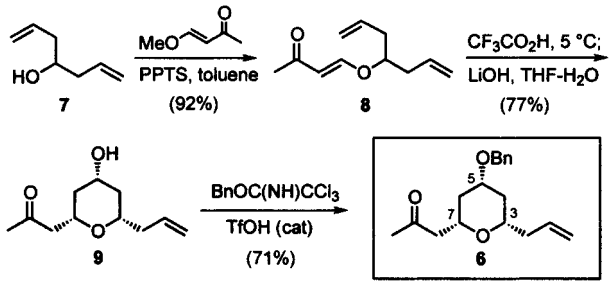
Scheme 1



C_9-carbonyl and hydrosilylation of the C_{12}-methylene. The resulting silacycle **3** was designed to reveal advanced fragment **2** upon cleavage of the C−Si and O−Si linkages. Highly convergent disconnection of ketone **4** at C_{10}−C_{11} furnished the corresponding aldol coupling partners **5** and **6.** According to the precedent recently provided by Paterson[7] and Evans,[8] boron-enolate mediated aldolization was expected to deliver the desired *anti*-stereochemical relationship between the newly created C_{11}-hydroxyl and C_7-alkoxy group. Aldehyde **5** would be rapidly assembled via an alkylation−formylation sequence (vide infra). Construction of ketone **6**, incorporating an all-*cis* trisubstituted tetrahydropyran subunit, would entail a highly diastereoselective Prins cyclization.[9]

Assembly of ketone **6** began with vinylogous transesterification[10] of 4-methoxy-3-butenone with heptadienol **7**[11]

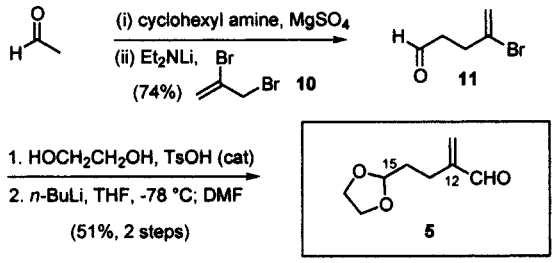
Scheme 2



(PPTS, toluene, 110 °C), furnishing the Prins cyclization precursor **8** in 92% yield (Scheme 2). Treatment of vinylogous ester **8** with TFA[12] at 5 °C followed by basic hydrolysis of the trifluoroacetate resulted in formation of the all-*cis* tetrahydropyran **9** in 77% yield.[13] Equatorial disposition of substituents was rigorously established at this stage by a combination of DQF COSY and NOESY experiments. The highly stereocontrolled construction of three stereogenic centers in a single step is illustrative of the power of Prins desymmetrization tactics for the assembly of polysubstituted tetrahydropyrans. Acid-catalyzed benzylation of alcohol **9** ($BnOC(NH)CCl_3$, TfOH (cat.), CH_2Cl_2−cyclohexane)[14] then afforded ketone **6**, completing construction of the first aldol coupling partner in three steps and 50% overall yield.

Preparation of aldehyde **5**, the second aldol component, was similarly accomplished in three steps (Scheme 3).

Scheme 3



Conversion of acetaldehyde to the corresponding cyclohexyl imine, followed by lithiation[15] and alkylation with 2,3-dibromopropene (**10**), afforded aldehyde **11** in 74% yield.[16] Acetalization (ethylene glycol, TsOH) and formylation via metal−halogen exchange, followed by addition of dimethylformamide, furnished aldehyde **5** in 38% overall yield for the three steps.

(7) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585−8588.

(8) (a) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788−789. (b) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671−8726. (c) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033−10046.

(9) For reviews and leading references, see: (a) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661−672. (b) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 527−561. (c) Yang, J.; Viswanathan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627−1630. (d) Cloninger, M.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092−1093. (e) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217−1219.

(10) Danishefsky, S. J.; Bednarski, M.; Izawa, T.; Maring, C. *J. Org. Chem.* **1984**, *49*, 2290−2292.

(11) Available from Aldrich Chemical Co.

(12) Nussbaumer, C.; Frater, G. *Helv. Chim. Acta* **1987**, *70*, 396−401.

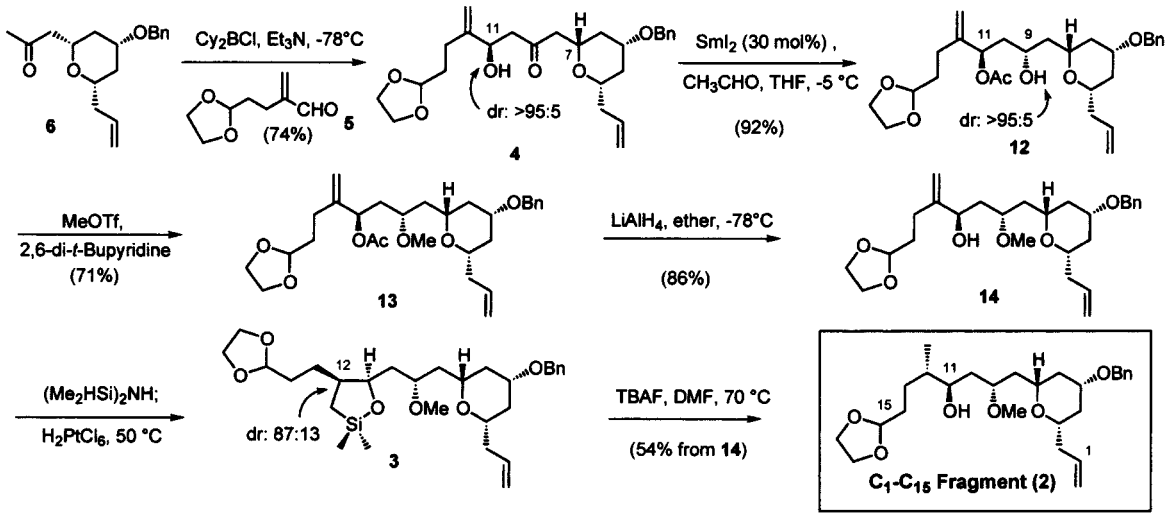
(13) A minor amount (7%) of the C_5 diastereomer was also isolated.

(14) Widmer, U. *Synthesis* **1987**, 568−570.

(15) Le Borgne, J. F. *J. Organomet. Chem.* **1976**, *122*, 129−137.

(16) Barnhart, R. W.; Wang, X.; Noheda, P.; Bergens, S. H.; Whelan, J. Bosnich, B. *J. Am. Chem. Soc.* **1994**, *116*, 1821−1830.

Scheme 4

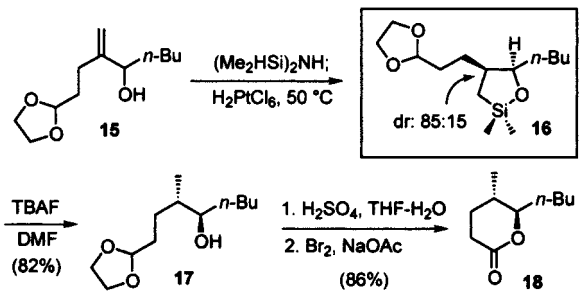


Generation of the dicyclohexylboron enolate from ketone **6** followed by addition of aldehyde **5** (−78 °C, ether)[7] efficiently accomplished the union of these aldol reaction partners, furnishing hydroxy ketone **4** as a single diastereomer (Scheme 4). Apart from the high convergency, this operation delivered the requisite stereochemistry of the newly created C_{11} alcohol as a result of efficient 1,5-*anti* stereochemical induction by the C_7-alkoxy group.[7,8]

Diastereoselective ketone reduction [SmI_2 (30 mol %), CH_3CHO, THF][17] cleanly established the C_9-stereogenic center (92% yield, dr >95:5). Methylation (MeOTf, 2,6-di-*tert*-butylpyridine),[18] followed by removal of the acetate with $LiAlH_4$, gave allylic alcohol **14** in 86% yield.

The validation of the projected late-stage hydrosilylation was initially achieved in a model study summarized in Scheme 5. Conversion of alcohol **15**[19] into the corresponding

Scheme 5



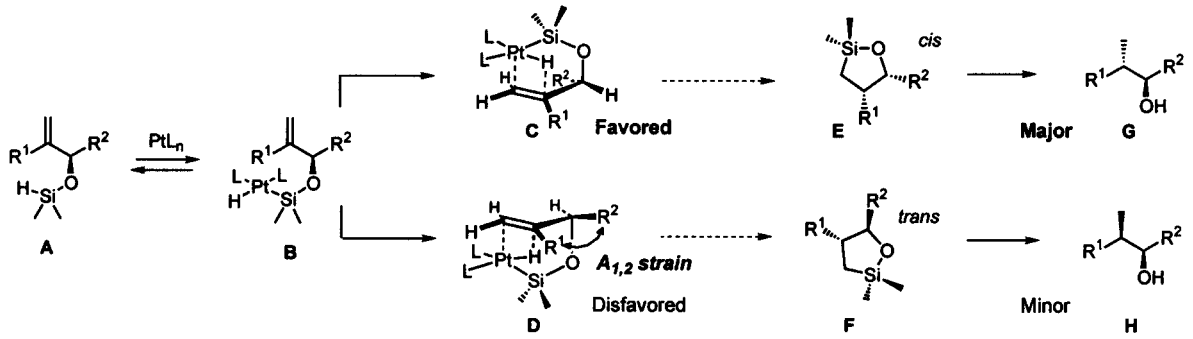
silyl ether using tetramethyldisilazane, followed by treatment with H_2PtCl_6 (0.3 mol %) in benzene at 50 °C, resulted in facile formation of silacycle **16** (dr 85:15). Importantly, no products resulting from competing olefin isomerization were detected. Stereochemical assignment of **16**, initially based on the precedent by Tamao,[20] was achieved by conversion to the known lactone **18**[21] involving protodesilylation (TBAF, DMF)[22] and acid-catalyzed acetal hydrolysis, followed by oxidation of the resulting lactol to the lactone (Br_2, NaOAc, $AcOH-H_2O$).[23]

Having established a reliable hydrosilylation protocol, attention was focused on conversion of alcohol **14** to subtarget **2** (Scheme 4). Silylation [$(Me_2HSi)_2NH$, $CHCl_3$, 15 min), followed by addition of H_2PtCl_6 (0.5 mol %), resulted in diastereoselective formation of silacycle **3** (dr 87:13) without detectable hydrosilylation of the terminal olefin. Protodesilylation was then achieved using TBAF (DMF, 70 °C, 15 min)[22] to give the fully elaborated C_1-C_{15} fragment (**2**) of leucascandrolide A.

The stereochemical outcome of the intramolecular hydrosilylation of alcohols **14** and **15** resulting in predominant formation of *anti*-diastereomeric products **2** and **17**, respectively, is in agreement with *erythro* selectivity previously observed by Tamao.[20] If hydroplatination is assumed to be a stereochemistry-determining step,[20c] examination of the diastereomeric transition structures **C** and **D** (Scheme 6) provides a rationale for the observed selectivity. Indeed, transition state **D** is expected to be higher in energy due to the unfavorable nonbonding interaction between R^1 and R^2 resulting in significant $A_{1,2}$-strain. Therefore, formation of

(17) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449.
(18) Walba, D. M.; Thurmes, W. H.; Haltiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046−1056.
(19) This compound was prepared in one step by addition of *n*-BuLi to aldehyde **5** (87% yield).
(20) (a) Tamao, K.; Nakajima, T.; Sumiiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6090−6093. (b) Tamao, K.; Yamauchi, T.; Ito, Y. *Chem Lett.* **1987**, 171−174. (c) Tamao, K.; Nakagawa, Y.; Ito, Y. *Organometallics* **1993**, *12*, 2297−2308. Also, see: (d) Bergens, S. H.; Noheda, P.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1992**, *114*, 2121−2128. (e) Bergens, S. H.; Noheda, P.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1992**, *114*, 2128−2135.
(21) Collum, D. B.; Mohamadi, F.; Hallock, J. S. *J. Am. Chem. Soc.* **1983**, *105*, 6882−6889.
(22) Hale, M. R.; Hoveyda, A. H. *J. Org. Chem.* **1992**, *57*, 1643−1645.
(23) Kocienski, P. J.; Street, S. D. A.; Yeates, C.; Campbell, S. F. *J. Chem. Soc., Perkin Trans.* **1987**, 2171−2181.

Scheme 6



the *cis*-disubstituted cyclic silane **E**, as the major product, proceeds through transition state **C** involving diastereoselective delivery of hydride from the *re*-face. Final cleavage of the O−Si and C−Si bonds reveals the observed *anti*-alcohol **G**.

In summary, the assembly of C_1−C_{15} fragment **2** of leucascandrolide A (**1**) has been achieved in nine steps and 11% overall yield. The six requisite stereogenic centers were assembled via a stereochemical relay featuring a series of highly diastereoselective processes including Prins desymmetrization, aldol condensation, and Pt-catalyzed hydrosilylation. Completion of the synthesis of leucascandrolide A, along with further applications of cyclic silanes for the development of new stereoselective transformations, are currently under active investigation and will be reported in due course.

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Supporting Information Available: Complete experimental procedures and spectral characterization of all new compounds. This material is available free of charge at http://pubs.acs.org.

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