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Enantioselective [4 + 2]-Annulation of Chiral Crotylsilanes: Application to the Synthesis of a C1–C22 Fragment of Leucascandrolide A

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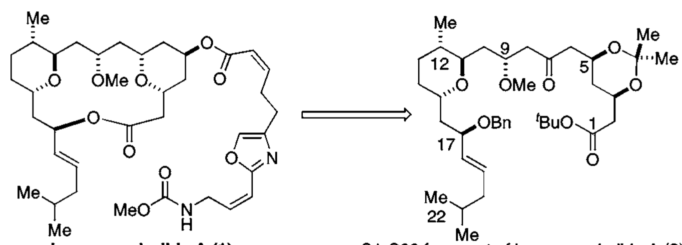
ABSTRACT



leucascandrolide A (1) C1-C22 fragment of leucascandrolide A (**2**)

The asymmetric synthesis of a C1–C22 fragment (2) of leucascandrolide A is described. Synthetic highlights include the construction of the C9–C22 pyran fragment using a formal [4 + 2]-annulation of a chiral organosilane. A diastereoselctive Mukaiyama aldol was used to introduce the C9 stereocenter and complete the assembly of the macrocycle's carbon skeleton.

Leucascandrolide A **1** is a doubly O-bridged 18-memebered macrolide isolated from the calcareous sponge *Leucascandra caveolata*, obtained from the northeastern coast of New Calendonia, Coral Sea.[1] This macrolide exhibits high in vitro cytotoxicity against human KB and P388 tumor cell lines displaying low IC_{50} values of 0.05 and 0.26 μg/mL, respectively. The natural product also possesses potent antifungal ability against *Candida albicans*, a pathogenic yeast that attacks AIDS patients and other immunocompromised individuals. A subsequent report indicates that leucascandrolide A is no longer available from its initial natural source.[2] It has been postulated that **1** is not a metabolite of *Leucascandra caveolata* but rather an opportunistic bacteria as evidenced by the large amounts of dead tissue in the initial harvest of *Leucascandra caveolata*. Currently there is no natural source of leucascandrolide A.

The lack of a natural source of **1**, together with its unique doubly oxygenated 18-membered macrolide, has made leucascandrolide A, a target of interest for the synthetic community. Following the first total synthesis by Leighton,[3] there have been additional reports detailing total,[4] formal,[5] and fragment syntheses of **1**.[6] Herein we discuss our approach

(1) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta*. **1996**, *79*, 51−60.

(2) (a) D'Ambrosio, M.; Tato, M.; Pocsfalvi, G.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 347−353. (b) D'Ambrosio, M.; Tato, M.; Pocsfalvi, G.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 1135.

(3) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc*. **2000**, *122*, 12894−12895.

(4) (a) Fettes, A.; Carreira, E. M. *Angew. Chem., Int. Ed*. **2002**, *41*, 4098−4101. (b) Paterson, I.; Tudge, M. *Angew. Chem., Int. Ed*. **2003**, *42*, 343−347. (c) Wang, Y.; Janic, J.; Kozmin, S. A. *J. Am. Chem. Soc*. **2002**, *124*, 13670−13671.

(5) (a) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **2001**, *123*, 8420−8421. (b) Wipf, P.; Reeves, J. T. *Chem. Commun*. **2002**, 2066−2067.

(6) (a) Crimmins, M. T.; Carroll, C. A.; King, B. W. *Org. Lett*. **2000**, *2*, 597−599. (b) Wipf, P.; Graham, T. H. *J. Org. Chem*. **2001**, *66*, 3242−3245. (c) Dakin, L. A.; Langille, N. F.; Panek, J. S. *J. Org. Chem*. **2002**, *67*, 6812−6815.

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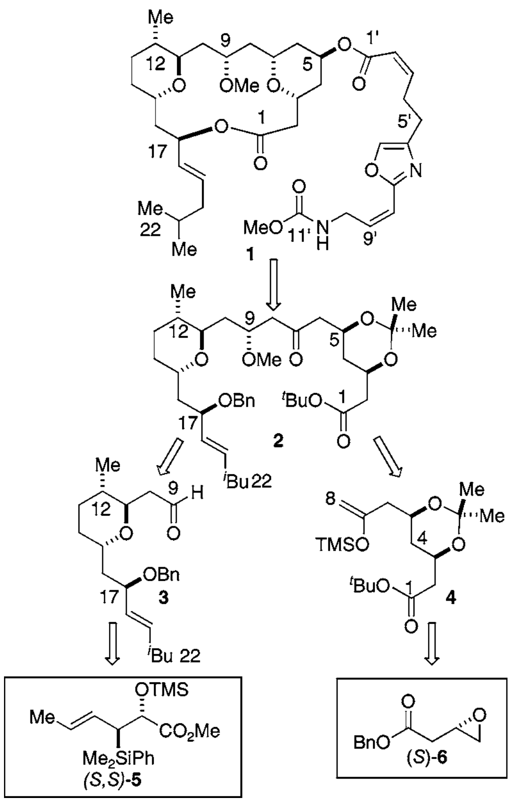
to macrolide and describe the synthesis of the C1−C22 advanced intermediate**.** Concerning the retrosynthesis of **1**, disconnection of the C5 ester gives the macrocyclic lactone, which could be derived from the C1−C22 fragment **2** (Scheme 1). Further analysis of **2** suggests that it could be

Scheme 1. Retrosynthetic Analysis of Leucascandrolide A



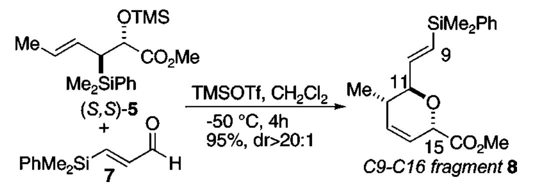
divided at the C8−C9 bond to give the Mukaiyama aldol-coupling partners: pyran **3** and silyl enol ether **4**.[7] The C9−C22 pyran **3** could be synthesized using the [4 + 2] annulation of chiral crotylsilanes developed in our laboratories between chiral silane (*S*,*S*)-**5** and an appropriate aldehyde.[8]

Silyl enol ether **4**, could be synthesized in a straightforward manner starting with enantioenriched epoxide (*S*)-**6** as an initial building block, readily available via Jacobsen's hydrolytic kinetic resolution (HKR).[9]

To begin the synthesis of fragment **3**, a [4 + 2] annulation of (*S*,*S*)-**5** with selected aldehydes capable of serving as a precursor to the C9 aldehyde was evaluated. After a brief examination of the reaction, it was determined that reaction of (*S*,*S*)-**5** with aldehyde **7** catalyzed by TMSOTf at −50 °C gave the requisite dihydropyran **8** in excellent yield (95%) and diastereoselctivity (dr > 20:1).[10]

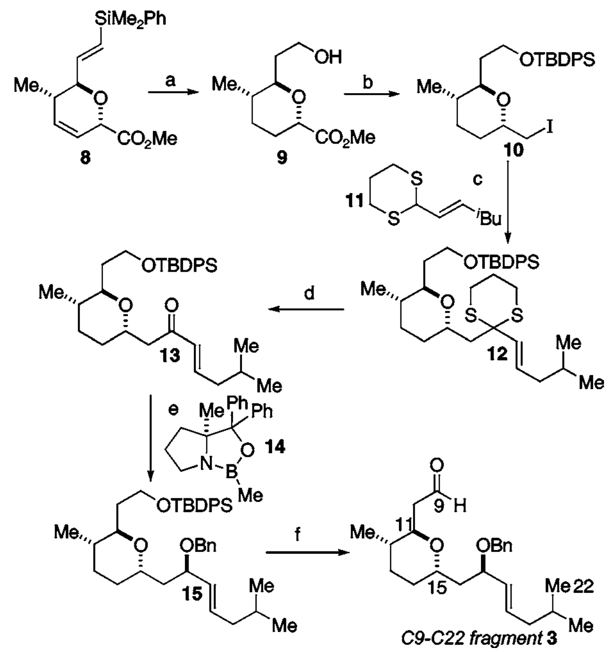
The utility of the annulation is illustrated in the efficient manner in which it installs the C11, C12, and C15 stereocenters of the target molecule (Scheme 2).

Scheme 2. Construction of the Left-Hand Pyran Subunit



With efficient access to dihydropyran **8**, construction of the aldehyde **3** was initiated (Scheme 3). Elaboration of **8**

Scheme 3. Synthesis of Pyran **3**[a]



[a] Key: (a) (i) H_2, Pd/C, EtOAc, rt, 99%; (ii) $Hg(OAc)_2$, CH_3CO_3H, rt, 76%. (b) (i) TBDPSCl, imidazole, DMF, rt; (ii) Dibal-H, CH_2Cl_2, 0 °C; (iii) $(PhO)_3P^+CH_3I^-$, DMF, 0 °C, 77% for three steps. (c) **11**, ^{t}BuLi, THF/HMPA (10:1), 78 → 0 °C, 97%. (d) Dess−Martin periodinane, MeOH/H_2O/THF (8:1:1), rt, 91%. (e) (i) (*S*)-CBS (**14**), BH_3·THF, THF, −20 °C, 80%, (dr > 15:1); (ii) NaH, BnBr, *n*-Bu_4NI, DMF, rt, 90%. (f) (i) TBAF, THF, rt, 99%; (ii) Dess−Martin periodinane, pyridine, CH_2Cl_2, rt, 80%.

began with the hydrogenation of the olefins under the standard conditions (H_2, Pd/C) followed by a Fleming−Tamao oxidation[11] of the dimethylphenylsilyl substituent. This was best performed by treatment with $Hg(OAc)_2$ in

(7) Mukaiyama, T.; Banno, K.; Naraska, N. *J. Am. Chem. Soc.* **1974**, *96*, 7503−7509.

(8) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836−9837.

(9) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E. Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1316.

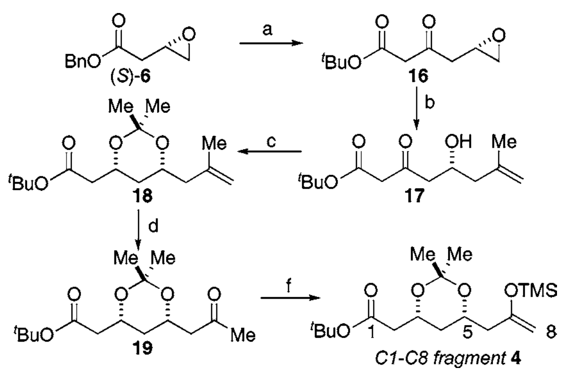
(10) Several other protected 3-hydroxy-propionaldehyde derivates were surveyed in the annulation with (*S*,*S*)-**5** all giving inferior yields and diastereoselectivities.

(11) (a) Fleming, I.; Henning, R.; Parker, D. C. Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin. Trans. 1* **1995**, 317−337. (b) Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984**, C37−C39.

peracetic acid giving alcohol **9** in 74% yield for two steps. Protection of the primary alcohol as the *tert*-butyldiphenylsilyether, Dibal-H reduction of the methyl ester to the primary alcohol, and subsequent treatment with $(PhO)_3P^+CH_3I^-$ in DMF gave alkyl iodide **10** (77% yield over three steps). Iodide **10** was then alkylated (97%) by treatment with the lithium anion of dithiane **11** in a THF/HMPA (10:1) solvent system.[12] At this stage it was necessary to unveil the α,β-unsaturated ketone **13**. This proved to be challenging, and after an extensive review of conditions that promote the removal of dithiane protecting groups, it was discovered that treamtent of **12** with Dess–Martin periodinane in wet methanol for 12 h afforded α,β-unsaturated ketone **13** in good yield.[13] Subsequent reduction of ketone **13** with a catalytic amount of Corey's chiral borane, (*S*)-CBS (**14**), in the presence of $BH_3{\cdot}SMe_2$, cleanly installed the C17 stereocenter (80%, dr $\approx$ 15:1).[14] Protection of the emerged allylic alcohol as the benzyl ether (BnBr, *n*-Bu_4NI, DMF, 90%) and deprotection of the primary silyl ether (TBAF, 99%), followed by Dess–Martin oxidation[15] of the resulting primary alcohol (80%), afforded the aldehyde, completing the synthesis of intermediate **3.**

Synthesis of the C1–C8 silyl enol ether **4** began with enantiomerically pure epoxide (*S*)-**6** readily available in multigram quantities from HKR of (±) **6** (Scheme 4).

Scheme 4. Synthesis of Silyl Enol Ether **4**[a]

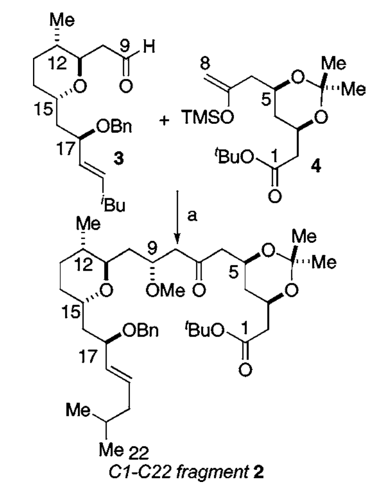


[a] Key: (a) *tert*-butyl acetate, LDA, THF, −50 °C, 70%. (b) Isopropenylmagnesium bromide, 20 mol % CuI, THF, −50 °C, 75%. (c) (i) $Zn(BH_4)_2$, CH_2Cl_2, −78 °C, 80%, dr > 15:1; (ii) 2,2-dimethoxypropane, cat. *p*-TsOH, rt, 99%. (d) O_3, MeOH, Me_2S, −78 °C, 95%. (e) Lithium tetramethylpiperidine, TMSCl, −78 °C, 77%.

Treatment of (*S*)-**6** with the lithium anion of *tert*-butyl acetate in THF at −50 °C gave the unstable β-ketoester **16** in 70% yield. Subsequent treatment of **16** with isopropenylmagnesium bromide in the presence of 20 mol % CuI provided β-hydroxy ketone **17** (75%). Subsequent treatment of **17** with $Zn(BH_4)_2$[16] in CH_2Cl_2 at −78 °C afforded a 1,3-syn reduction to the 1,3-diol (80%, dr > 15:1). This material was then treated with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-TsOH, which provided acetonide **18**. Completion of **4** was accomplished by cleavage of the terminal olefin by ozonolysis giving ketone **19**, which, when treated the bulky lithium anion of 2,2,6,6-tetramethylpiperidine, gave the desired regiochemical enolate, which was then trapped with TMS–Cl, completing the C1–C8 silyl enol ether coupling partner **4**.

To undertake the assembly of the C1–C22 fragment **2**, a Mukaiyama aldol between aldehyde **3** and silyl enol ether **4** was investigated. After a brief survey of the reaction, it was determined that the coupling was best effected by treatment of a mixture of **3** and **4** in CH_2Cl_2 with $BF_3{\cdot}OEt_2$ at −78 °C for 4 h (Scheme 5). Gratifyingly, the coupling proceeded in good yield (81%) and diastereoselectivity (dr > 15:1). Despite the monodentate nature of $BF_3{\cdot}OEt_2$, there is ample precedent for 1,3-anti induction in similar systems.[17] The absolute stereochemistry at C9 was unambiguously assigned using the method of Mosher.[18] The methylation of the C9 hydroxyl was then accomplished by treatment with Meerwein's reagent and Proton sponge (99%) giving the C1–C22 fragment **2**.[19]

Scheme 5. Synthesis of the C1–C22 Fragment **2**[a]



[a] Key: (a) (ii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 81% dr > 15:1; (ii) Me_3OBF_4, Proton Sponge, 4 Å molecular sieves, CH_2Cl_2, rt, 99%.

(12) For leading references on dithiane alkylation, see: Smith, A. B.; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925–6926. and references therein.

(13) For an initial communication and discussion of this reaction, see: Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, *4*, 575–578.

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In conclusion, we have described a convergent synthesis to an advanced intermediate of leucascandrolide A. The approach features an enantioselective synthesis of the C9−C22 fragment **3** through the use of a formal [4 + 2] annulation between chiral crotylsilane (*S*,*S*)-**5** and aldehyde **6** and a 1,3-anti diastereoselective Mukaiyama aldol coupling between fragments **3** and **4**, which completed the carbon framework of the macrocycle of leucascandrolide A. Studies toward the completion of leucascandrolide A are underway and will be reported at a later time.

(19) Meerwein, H.; Hinz, G.; Hofmann, P.; Kroning, E.; Pfeil, E. *J. Prakt. Chem*. **1937**, *147*, 257.

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Supporting Information Available: General experimental procedures, including spectroscopic characterization of novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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