Total Synthesis of Leucascandrolide A

Keith R. Hornberger, Christopher L. Hamblett, and James L. Leighton*

Department of Chemistry
Columbia University
New York, New York, 10027

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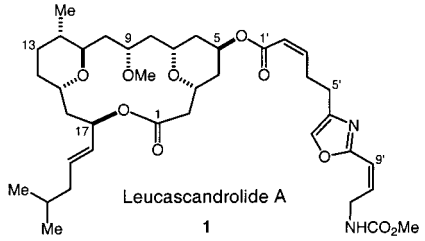
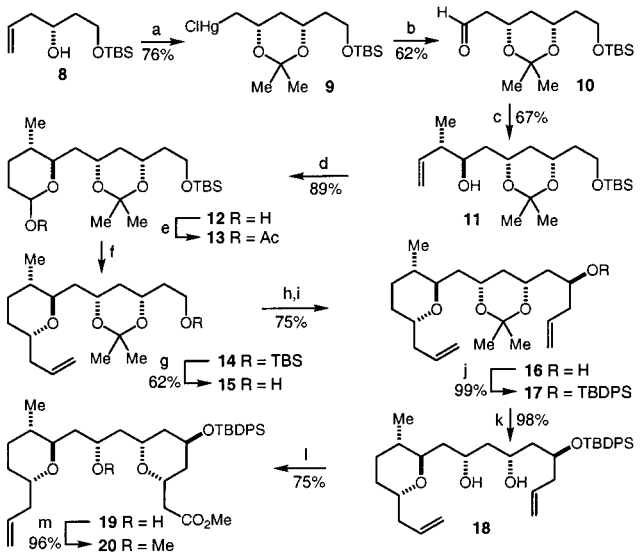
Leucascandrolide A (**1**) was isolated from the sponge *Leucascandra caveolata* by Pietra and co-workers in 1996.[1] The natural product displays strong in vitro cytotoxicity against KB and P388 cancer cell lines and is also a potent antifungal, inhibiting the growth of *Candida albicans*. The unusual molecular achitecture of **1**, consisting of a doubly O-bridged 18-membered macrolide,



coupled with its biological activity, makes it an attractive target for total synthesis.[2] In fact, the specific biological source of leucascandrolide is currently unknown, and thus total synthesis is currently the *only* potential source of this intriguing molecule. Herein we report an enantioselective total synthesis of leucascandrolide A.

The synthesis of leucascandrolide A commenced from known homoallylic alcohol **8**[3] (Scheme 1). $Yb(OTf)_3$-catalyzed oxymercuration with HgClOAc in acetone furnished organomercury chloride **9** in 76% yield.[4] Rh(I)-catalyzed formylation of **9** in the presence of 0.50 equiv of1,4-diazabicyclo[2.2.2]octane (DABCO) then afforded aldehyde **10** in 62% yield.[5] Crotylation of **10** according to the protocol of Brown[6] provided alkene **11** in 67% yield and with >10:1 diastereoselectivity. Regioselective Rh(I)-catalyzed hydroformylation of **11** gave a ∼1:1 mixture of hemiacetals **12** in 89% yield. Treatment of **12** with Ac_2O, pyridine, and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 gave unstable acetate **13** as a mixture of diastereomers. Treatment of **13** with allyltrimethylsilane and $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ in CH_2Cl_2 at −78 °C afforded tetrahydropyran **14** (>10:1 ds).[7] After removal of the TBS group with tetra-*n*-butylammonium fluoride (TBAF), alcohol **15** was isolated in 62% yield over three steps from **12**. Swern oxidation[8] of **15** and Brown allylation[9] (>10:1 diastereoselectivity) of the resultant aldehyde afforded homoallylic alcohol **16** in 75% yield (two steps) from alcohol **15**.

Scheme 1[a]



[a] (a) HgClOAc, acetone, 5 mol% $Yb(OTf)_3$, 0 °C to rt. (b) 4 mol% $Rh(acac)(CO)_2$, 4 mol% $P(O\text{-}o\text{-}t\text{-}BuPh)_3$, 0.50 equiv DABCO, 800 psi 1:1CO/H_2, EtOAc, 50 °C. (c) (*E*)-crotyl-(−)-diisopinocampheylborane, $BF_3{\cdot}OEt_2$, THF, −78 °C; NaOH, H_2O_2, (d) 2 mol% $Rh(acac)(CO)_2$, 8 mol% PPh_3, 400 psi 1:1 CO/H_2, THF, 50 °C. (e) Ac_2O, DMAP, pyridine, CH_2Cl_2. (f) $H_2C{=}CHCH_2SiMe_3$, $Ti(O\text{-}i\text{-}Pr)_2Cl_2$, CH_2Cl_2, −78 °C. (g) *n*-Bu_4NF, THF. (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to −40 °C. (i) allyl-(−)-diisopinocampheylborane, Et_2O, −78 °C to rt; NaOH, H_2O_2. (j) TBDPSCl, imidazole, DMF. (k) AcOH, H_2O, 40 °C. (l) 10 mol% $PdCl_2$, 4 equiv $CuCl_2$, 1 atm CO, MeOH:PhCN (1:1). (m) Me_3OBF_4, Proton Sponge, 4 Å molecular seives, CH_2Cl_2.

Protection of alcohol **16** as the corresponding *tert*-butyldiphenylsilyl (TBDPS) ether[10] gave **17** in 99% yield, and hydrolysis (AcOH, H_2O, 40 °C) of the acetonide then afforded diol **18** in 98% yield and set the stage for the third carbonylation reaction in the sequence. Intramolecular alkoxycarbonylation according to the Semmelhack protocol (cat. $PdCl_2$, $CuCl_2$, 1 atm CO, 1:1 MeOH:PhCN) proceeded smoothly to provide the desired 2,6-*cis*-tetrahydropyran **19** in 75% yield and >10:1 diastereoselectivity.[11] In the course of optimizing this reaction, we have found that the use of benzonitrile as a cosolvent with methanol leads to cleaner and more efficient reactions. Strategically, the reaction is noteworthy in that the two alcohols and the two alkenes in **18** have been differentiated, significantly simplifying the protecting-group strategy. Finally, methylation of alcohol **19** with Me_3OBF_4 in the presence of 4 Å molecular sieves furnished methyl ether **20** in 96% yield.[12] The synthesis of **20** thus proceeds in 13 steps and 10% overall yield from alcohol **8**, employing three different carbonylation reactions.

The completion of the synthesis of the macrolide necessitated the diastereoselective addition of a vinylmetal fragment to a C(17) aldehyde. Toward this end, alkene **20** was subjected to ozonolysis to give aldehyde **21** in 93% yield (Scheme 2). Hydroboration of 4-methyl-1-pentyne with Cy_2BH, followed by transmetalation with Et_2Zn and addition of *N*,*N*-dibutylaminoethanol and $Ti(O\text{-}i\text{-}Pr)_4$, and addition of the resultant organozinc reagent to aldehyde **21**

(1) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51−60.
(2) For another approach to the synthesis of leucascandrolide A, see: Crimmins, M. T.; Carroll, C. A.; King, B. W. *Org. Lett.* **2000**, *2*, 597−599.
(3) Paterson, I.; Wallace, D. J.; Gibson, K. R. *Tetrahedron Lett.* **1997**, *38*, 8911−8914.
(4) (a) Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 403−405. (b) Dreher, S. D.; Hornberger, K. R.; Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 3197−3199.
(5) Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 3205−3208.
(6) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570−1576.
(7) (a) Lewis M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976−4978. (b) Danishefsky, S. J.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3803−3805. (c) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1983**, *24*, 1563−1566. (d) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383−2386. (e) Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479−1482.
(8) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.
(9) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432−439.
(10) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975−2977.
(11) (a) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496−1498. (b) Semmelhack M. F.; Kim, C.; Zhang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure Appl. Chem.* **1990**, *62*, 2035−2040. (c) White, J. D.; Hong, J.; Robarge, L. A. *Tetrahedron Lett.* **1999**, *40*, 1463−1466.
(12) Ireland, R. E.; Liu, L.; Roper, T. D.; Gleason, J. L. *Tetrahedron* **1997**, *53*, 13257−13284 and references therein.

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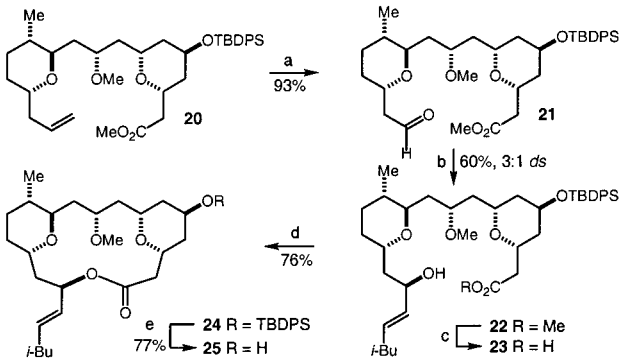
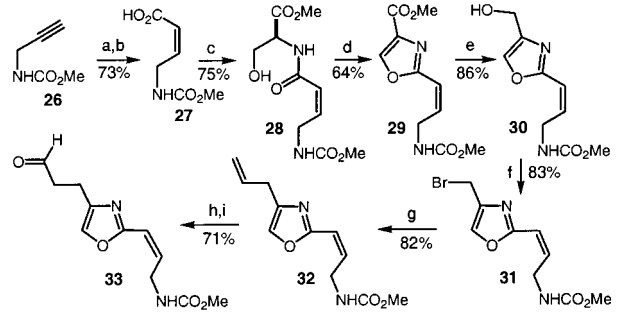
Scheme 2[a]



[a] (a) O_3, CH_2Cl_2, −78 °C; PPh_3, rt. (b) 4-Methyl-1-pentyne, Cy_2BH, Et_2Zn, *N*,*N*-dibutylaminoethanol, Ti(O-*i*-Pr)$_4$, toluene, −40 to −20 °C. (c) $KOSiMe_3$, Et_2O. (d) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, PhH. (e) TBAF, THF.

Scheme 3[a]

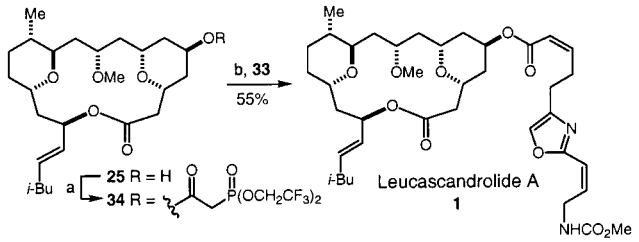


[a] (a) *n*-BuLi, CO_2, THF, −78 °C to 0 °C. (b) Lindlar's catalyst, quinoline, 1 atm H_2, EtOAc. (c) *i*-BuOCOCl, N-Me-Morpholine, Ser-OMe·HCl, THF. (d) DAST, CH_2Cl_2, −20 °C; $BrCCl_3$, DBU, 0 °C. (e) DIBAl-H, THF, 0 °C. (f) CBr_4, PPh_3, 2,6-lutidine, CH_3CN. (g) *n*-$Bu_3SnCH{=}CH_2$, Pd_2dba_3, tri(2-furyl)phosphine, THF, reflux. (h) 9-BBN, THF, H_2O_2. (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to 0 °C.

produced a 3:1 mixture of the desired allylic alcohol **22** and the corresponding diastereomer in 60% yield.[13] Demethylation of ester **22** with potassium trimethylsilanolate[14] provided seco-acid **23**, which was immediately subjected to macrolactonization, according to the Yonemitsu-modified Yamaguchi protocol[15] to afford macrolide **24** in 76% yield (two steps). Finally, **24** was subjected to the action of TBAF to provide alcohol **25** in 77% yield, ready for attachment of the acyl side chain. Macrolide **25** is a known compound synthesized from leucascandrolide A by Pietra and co-workers,[1] and full spectral comparison at this stage confirmed the structure of our synthetic material as well as the assignment of absolute configuration.

The synthesis of the side chain began with carbamate **26**, readily prepared from propargylamine and methyl chloroformate in 93% yield. Deprotonation with *n*-BuLi and quenching with CO_2 afforded the ynoic acid, which was immediately subjected to Lindlar reduction to give *Z*-enoic acid **27** in 73% yield over two steps (Scheme 3). Coupling of acid **27** to L-serine methyl ester via the mixed anhydride formed with isobutyl chloroformate produced amide **28** in 75% yield. This amide was readily converted to oxazole **29** in 64% yield by employing the recently

Scheme 4[a]



[a] (a) $(CF_3CH_2O)_2P(O)CH_2CO_2H$, EDCI·HCl, HOBt·$H_2O$, CH_2Cl_2. (b) KHMDS, 18-crown-6·CH_3CN, THF, −100 °C.

disclosed one-pot method of Wipf and Williams (diethylaminosulfurtrifluoride (DAST); DBU; $BrCCl_3$).[16] Reduction of the ester with DIBAL-H produced alcohol **30** (86% yield), which was then treated with CBr_4 and PPh_3 in CH_3CN to give bromide **31** in 83% yield. Stille coupling[17] with vinyltributyltin, catalyzed by Pd_2dba_3 modified by tri(2-furyl)phosphine[18] then produced allyloxazole **32** in 82% yield. Hydroboration (9-BBN) of the monosubstituted alkene and oxidation of the resultant alcohol under the conditions of Swern[8] gave aldehyde **33** in 71% yield over two steps. The synthesis of aldehyde **33** proceeds in 10 steps and 14% overall yield from propargylamine.

In anticipation of a Horner-Emmons reaction using Still's modification[19] to establish the *cis* enoate of the side chain, alcohol **25** was acylated with bis(2,2,2-trifluoroethyl)phosphonoacetic acid, employing 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI·HCl) and 1-hydroxybenzotriazole hydrate (HOBt·H_2O) to give phosphonoacetate **34**,[20] which was used immediately (Scheme 4). Deprotonation of **34** with potassium bis(trimethylsilyl)amide (KHMDS) at −78 °C in THF in the presence of 18-crown-6, and treatment of the resulting anion with aldehyde **33** at −100 °C gave a 7:1 mixture of fully synthetic leucascandrolide A **1** and the corresponding *E*-olefin isomer in 55% overall yield (two steps from **25**). The spectral properties (^1H and ^{13}C NMR, IR, optical rotation, MS) of our fully synthetic material matched the reported data for natural **1**.[21]

This synthesis of leucascandrolide A proceeds in 20 steps (longest linear sequence) from known alcohol **8** and provides a direct confirmation of the assignment of the absolute configuration of leucascandrolide A. It is amenable to the synthesis of structural variants and highlights the utility of the carbonylation-based approach to the synthesis of polyol and polyol-derived natural products.

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Supporting Information Available: Experimental procedures and spectral data for **9**−**11**, **15**−**22**, **24**−**33**, and **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Srebnik, M. *Tetrahedron Lett.* **1991**, *32*, 2449−2452. (b) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170−173. (c) Soai, K.; Takahashi, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1257−1258. (d) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691−5700.

(14) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831−5834.

(15) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993. (b) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367−6370.

(16) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165−1168.

(17) For reviews, see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (b) Mitchell, T. N. *Synthesis* **1992**, 803−815.

(18) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.

(19) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408.

(20) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597−5598.

(21) We thank Professor F. Pietra and co-workers for providing copies of their ^1H and ^{13}C NMR spectra of natural **1** and **25**.