extraction of Zn^{II} but not Cd^{II}. The highest selectivity with single ligands (Table 1) are 7.6-fold (**6**) and 3.1-fold (**8**). Interestingly both **6** and **8** are ketone-derived ligands with 2-aryl substituents, suggesting that this combination of substituents enhances extraction of Zn^{II}.

These studies demonstrate that dynamic combinatorial chemistry is a useful tool for the discovery of new metal ion complexes. Synergistic interactions of ligands are useful for building in selectivity for metal ions by using simple ligand substituent effects. This method has potential for practical applications given that the ligands are inexpensive and readily synthesized. However, there remains much to learn about the construction of an effective library of metal ion complexes. Future work will focus on exploring strategic positions for substitutents on different types of ligands and on increasing the complexity of the library by using metal complexes that bind three ligands.

Experimental Section

Extraction solutions were stirred in foil-wrapped vials with teflon-lined crimp caps for 2 h and were analyzed for Zn^{II} or Cd^{II} by use of dithizone indicator.[8] Standard deviations in measurements are 10% or less.

Acylhydrazone ligands were prepared by heating a solution of either 2-pyridinecarboxaldehyde (PCA) or 2-acetylpyridine in ethanol, a stoichiometric amount of the corresponding acylhydrazide, and a few drops of hydrochloric acid. Concentration of the solution and cooling followed by recrystallization from ethanol or ethanol/hexane yielded the ligand. In a typical preparation, benzoic hydrazide (0.272 g, 2.00 mmol) was added to a solution of PCA (0.190 mL, 2.00 mmol) in ethanol (20 mL) and a few drops of hydrochloric acid was added. The solution was gently heated and stirred for 0.25 h. Upon cooling, a white precipitate (**1**) formed, which was washed with ethanol, recrystallized, and dried in vacuo. ^{1}H NMR (400 MHz, [D_6]DMSO, 24 °C, TMS): $\delta = 12.0$ (s, 1H; NH), 8.60 (d, $^3J(H,H) = 4$ Hz,1H; H10), 8.46 (s, 1H; H6), 7.92 (m, 4H; H7, H8, H1, H5), 7.60 (t, $^3J(H,H) =$ 4.2 Hz, 1H; H9), 7.53 (t, $^3J(H,H) = 4.7$ Hz, 2H; H2, H4), 7.40 ppm (t, $^3J(H,H) = 5.6$ Hz, 1H; H3) (see Supporting Information for ligand-numbering scheme); ESI-MS: *m/z* (%): 226(52) [PCA-BAH+H^+], 248(100) [PCA-BAH+Na^+].

[$Zn(\mathbf{1}^-)_2$] was prepared by dissolving $Zn(NO_3)_2$ (0.788 g, 2.65 mmol) in hot ethanol (100 mL), followed by the addition of PCA (5.30 mmol), and benzoic hydrazide (0.721 g, 5.30 mol). Triethylamine (5.30 mmol) was added and the solution was heated to boiling for 0.25 h. Upon cooling, a bright yellow precipitate was recovered and recrystallized from ethanol. ^{1}H NMR (400 MHz, [D_1]chloroform, 25 °C, TMS): $\delta = 8.50$ (s, 1H; H6), 8.21 (d, $^3J(H,H) = 7.6$ Hz, 2H; H1, H5), 8.06 (d, $^3J(H,H) = 4.8$ Hz, 1H; H10), 7.72 (t, $^3J(H,H) = 7.6$ Hz,1H; H8), 7.38 (m, 4H; H9, H2, H4, H7), 7.14 ppm (t, $^3J(H,H) = 5.2$ Hz, 1H; H3); ESI MS: *m/z* (%): 513(100), 514(32), 515(63), 516(29), 517(44), [Zn(PCA-BAH)$_2$+H^+].

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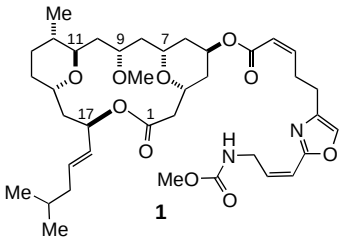
[1] J.-M. Lehn, *Chem. Eur. J.* **1999**, *5*, 2455 – 2463.
[2] P. A. Brady, J. K. M. Sanders, *J. Chem. Soc. Perkin Trans. 1* **1997**, 3237 – 3253.
[3] O. Storm, J. Lüning, *Chem. Eur. J.* **2002**, *8*, 793 – 798.
[4] V. Goral, M. I. Nelen, A. V. Eliseev, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 1347 – 1352.
[5] I. Huc, M. J. Krische, D. P. Funeriu, J.-M. Lehn, *Eur. J. Inorg. Chem.* **1999**, 1415 – 1420.
[6] B. Klekota, M. H. Hammond, B. L. Miller, *Tetrahedron Lett.* **1997**, *38*, 8639 – 8642.
[7] C. M. Karan, B. L. Miller, *J. Am. Chem. Soc.* **2001**, *123*, 7455 – 7456.
[8] D. M. Epstein, S. Choudhary, M. R. Churchill, K. Keil, A. V. Eliseev, J. R. Morrow, *Inorg. Chem.* **2001**, *40*, 1591 – 1596.
[9] J. Rydberg, T. Sekine in *Principles and Practices of Solvent Extraction* (Eds.: J. M. Rydberg, C. Musikas, G. R. Choppin), Marcel Dekker, New York, **1992**, pp. 101 – 156.
[10] G. R. L. Cousins, S.-A. Poulsen, J. K. M. Sanders, *Chem. Commun.* **1999**, 1575 – 1576.
[11] G. R. L. Cousins, R. L. E. Furlan, Y.-F. Ng, J. E. Redman, J. K. M. Sanders, *Angew. Chem.* **2001**, *113*, 437 – 442; *Angew. Chem. Int. Ed.* **2001**, *40*, 423 – 428.
[12] R. L. E. Furlan, G. R. L. Cousins, J. K. M. Sanders, *Chem. Commun.* **2000**, 1761 – 1762.
[13] T. Bunyapaiboonsri, O. Ramstrom, S. Lohmann, J.-M. Lehn, L. Peng, M. Goeldner, *ChemBioChem* **2001**, *2*, 438 – 444.
[14] M. L. Dietz, A. H. Bond, B. P. Hay, R. Chiarizia, V. J. Huber, A. W. Herlinger, *Chem. Commun.* **1999**, 1177 – 1178.
[15] Y. Sasaki, G. R. Choppin, *J. Radioanal. Nucl. Chem.* **1997**, *222*, 271 – 274.
[16] D. A. J. Voss, L. A. Buttrey-Thomas, T. S. Janik, M. R. Churchill, J. R. Morrow, *Inorg. Chim. Acta* **2001**, *317*, 149 – 156.

Total Synthesis of Leucascandrolide A**

Alec Fettes and Erick M. Carreira*

Leucascandrolide A (**1**), a polyoxygenated marine macrolide of a new genus, was isolated in 1996 by Pietra and co-



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workers from the calcareous sponge *Leucascandra caveolata* along the east coasts of New Caledonia.[1] Despite subsequent intensive efforts, later expeditions failed to provide additional leucascandrolide A.[2] Leucascandrolide A (**1**) displays strong cytotoxic activity in vitro on human KB and P388 cancer cell lines ($IC_{50} = 50$ and 250 ng mL^{-1}, respectively) as well as powerful antifungal activity. An elegant total synthesis has been recently reported by Leighton and co-workers,[3] and a formal synthesis has been documented by Rychnovsky and co-workers[4] along with synthetic studies of the core by Crimmins et al.[5] and Kozmin[6] and a synthesis of the oxazole side chain by Wipf et al.[7] The lack of availability of

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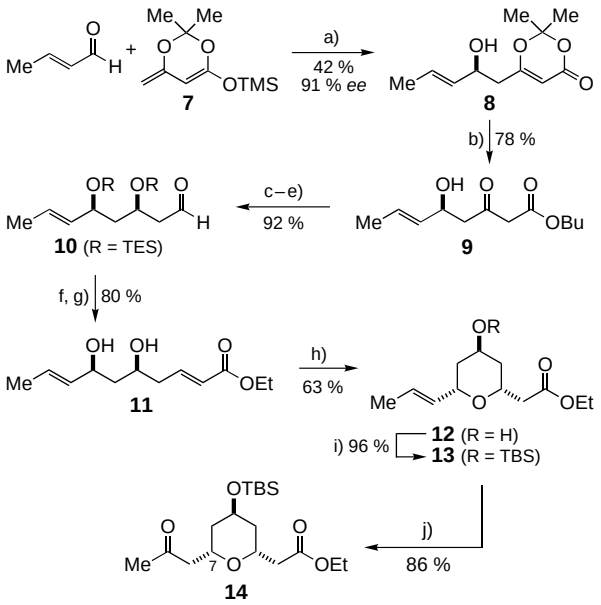
Leucascandrolide A (**1**) from natural sources, its powerful biological activity as well as its unusual structure compelled us to embark on a program aimed at its total synthesis. Herein, we describe a concise, stereocontrolled, enantioselective total synthesis of the natural product which is realized through the application of modern enantio- and diastereoselective methods for asymmetric synthesis.

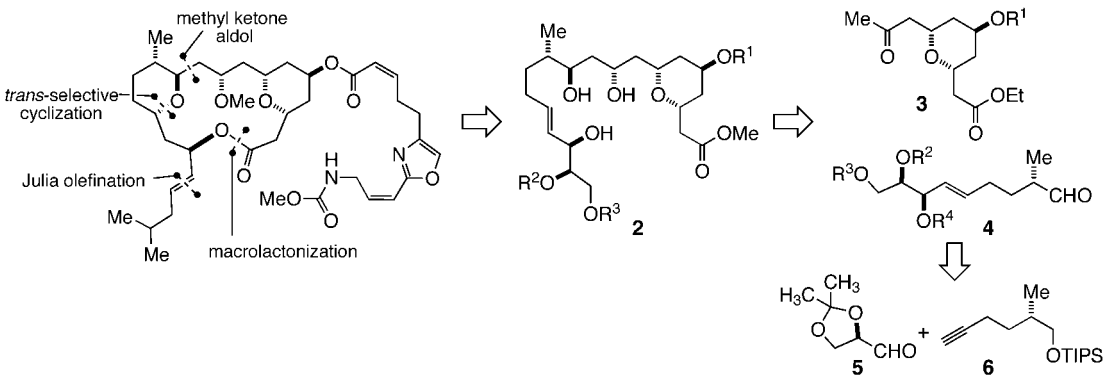
In our retrosynthetic strategy, we envisioned macrolactonization and late-stage introduction of the C17 side chain (Scheme 1). Additionally, the 2,6-*trans*-substituted tetrahydropyran would require a *trans*-selective intramolecular oxidative cyclization of a 6-hydroxy alkene. Cyclization retron **2** would be derived from methyl ketone **3** and aldehyde **4** by stereoselective aldol addition. The key building block **4** could be conveniently assembled by employing (*R*)-isopropylidene glyceraldehyde (**5**) and acetylene **6** by using a method we have described recently.[8]

The synthesis of methyl ketone **14** commences with the enantioselective addition of trimethylsilyl dienolate **7** to crotonaldehyde catalyzed by our (*R*)-Tol-BINAP copper(I) fluoride complex (2 mol%) to give aldol adduct **8** in 42% yield and 91% *ee* (by HPLC) (Scheme 2).[9] The C=O addition reactions of crotonaldehyde are typically executed only with some difficulty, because of its susceptibility towards polymerization; thus, formation of product **8** in high levels of enantioselectivity is noteworthy. When adduct **8** was heated at reflux in *n*-butanol, keto ester **9** was isolated (78%), which, following *syn* reduction,[10] protection of the corresponding diol, and semireduction of the butyl ester with DIBAL-H in toluene, furnished aldehyde **10** (92% over 3 steps). Horner-Wadsworth-Emmons olefination under the conditions developed by Roush and Masamune[11] followed by deprotection of the silyl ethers afforded **11** (80% over 2 steps). This diol ester was observed to undergo cyclization readily upon treatment with catalytic amounts of *t*BuOK to give the thermodynamically favored 2,6-*syn*-disubstituted tetrahydropyran **12** in 63% yield.[12] The free secondary alcohol was then protected to furnish silyl ether **13** (96%). Further elaboration of this intermediate to methyl ketone **14** necessitated the execution of a regioselective Wacker oxidation, which would need to proceed without jeopardizing the stereocenter at C7.[13] We were pleased to discover that **13** participated in a high-yielding, highly regioselective Wacker oxidation reaction that gave access to the desired methyl ketone **14** in 86% yield. It is worth noting that this advanced intermediate possesses one of the tetrahydropyran rings found in the natural product with attendant stereocenters and, importantly, is accessed in nine steps and 30% overall yield from **8**.



Scheme 2. a) (*R*)-Tol-BINAP (2.1 mol%), $Cu(OTf)_2$ (2.0 mol%), $Bu_4NPh_3SiF_2$ (4.0 mol%), THF, −78°C, then **7** and crotonaldehyde, 4 h, then TFA, 42%; b) *n*BuOH, reflux, 1 h, 78%; c) $NaBH_4$, Et_3B, MeOH, THF, −78°C, 5 h; d) TESCl, imid., DMAP, DMF, RT, 12 h; e) DIBAL-H, toluene, −78°C, 30 min, 92% (3 steps) (d.r. > 95:5); f) DBU, LiCl, $(EtO)_2P(O)CH_2CO_2Et$, CH_3CN, RT, 2 h; g) TBAF, THF, RT, 2 h, 80% (2 steps); h) *t*BuOK (10 mol%), THF, 0°C, 63% (d.r. 10:1); i) TBSCl, imid., DMAP, DMF, RT, 96%; j) $PdCl_2$ (20 mol%), CuCl, O_2, DMF/H_2O 7:1, RT, 86%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIBAL-H = diisobutylaluminium hydride, DMAP = 4-*N*,*N*-dimethylamino pyridine, imid. = imidazole, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TFA = trifluoroacetic acid, TMS = trimethylsilyl, (*R*)-Tol-BINAP = (*R*)-2,2′-Bis(di-*p*-tolyl-phosphino)-[1,1′]-binaphthyl.

The next key intermediate, aldehyde **19**, was conveniently prepared starting from known alcohol **15** (Scheme 3).[14] Oxidation of **15** to the corresponding aldehyde (TEMPO/bleach) was followed by conversion to terminal alkyne **6** in 87% yield according to the Bestmann–Roth protocol.[15] The addition of **6** to (*R*)-isopropylidene glyceraldehyde (**5**)[16] was effected employing the method we have recently developed for the in situ generation of Zn-alkynilides under mild conditions. In the context of this project we aimed to establish



Scheme 1. Retrosynthetic Analysis. TIPS = triisopropylsilyl.

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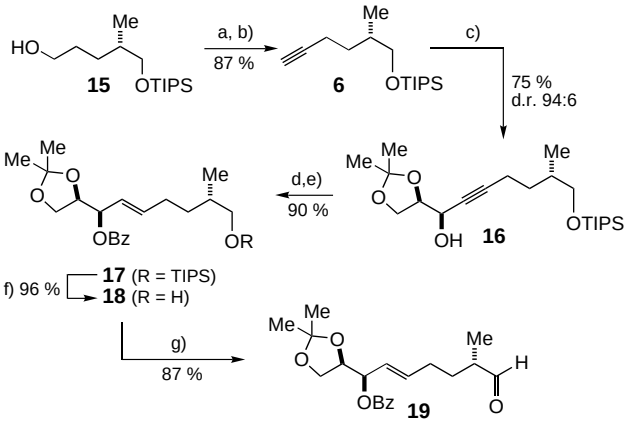
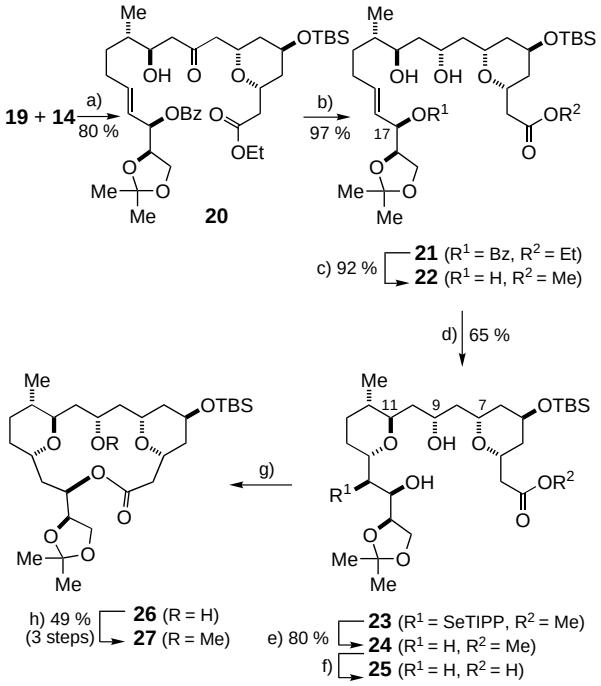


Scheme 3. a) TEMPO, bleach, KBr, CH_2Cl_2, pH 8.6 buffer, RT, 15 min; b) $(MeO)_2P(O)CN_2CO_2CH_3$, K_2CO_3, MeOH, 16 h, RT, 87 % (2 steps); c) $Zn(OTf)_2$, (−)-*N*-methylephedrine, Et_3N, toluene, then **5**, RT, 48 h, 75 % (d.r. 94:6); d) $LiAlH_4$, THF, RT, 5 h; e) BzCl, Et_3N, DMAP, CH_2Cl_2, RT, 15 h, 90 % (2 steps); f) TBAF, THF, 0 °C→RT, 24 h, 96 %; g) TPAP, NMO, CH_2Cl_2, RT, 30 min, 87 %. Bz = benzoyl, NMO = *N*-methyl morpholine *N*-oxide, TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl, TPAP = tetrapropylammonium perruthenate.



Scheme 4. a) Bu_2BOTf, Et*i*Pr_2N, Et_2O, −78 °C, then **19**, 5 h, 80 % (d.r. > 95:5); b) TABH, AcOH, CH_3CN, −40 °C, 70 h, 97 % (d.r. > 95:5); c) K_2CO_3, MeOH, RT, 40 h, 92 %; d) TIPPSeBr, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, −78 °C, 74 % (d.r. 88:12); e) 2,4-dimethoxy-3-methyl-3-*tert*-butyldimethylsilylcyclohexa-1,4-diene, AIBN, *n*-hexane, reflux, 1 h, 80 %; f) TMSOK, Et_2O, RT, 24 h; g) 2,4,6-trichlorobenzoylchloride, Et_3N, DMAP, DMF, RT; h) Me_3OBF_4, proton sponge, 4 Å M.S., CH_2Cl_2, RT, 49 % (3 steps). AIBN = 2,2′-azoisobutyronitrile, M.S. = molecular sieves, proton sponge = *N*,*N*,*N*′,*N*′-tetramethyl-1,8-diaminonaphthalene, TABH = tetramethylammonium triacetoxy borohydride, TIPP = 2,4,6-triisopropylphenyl.

whether the reaction could be executed in a reagent-controlled manner with a chiral aldehyde possessing a stereogenic center at C_α.[17] In this respect, we were delighted to find that **6**, upon treatment with $Zn(OTf)_2$, (−)-*N*-methylephedrine, and Et_3N in toluene, cleanly adds to **5** to give propargylic alcohol **16** in 75 % yield and 94:6 diastereoselectivity. Adduct **16** was converted to allylic benzoate (*E*)-**17** by reduction with lithium aluminum hydride followed by benzoylation (90 % over two steps). Desilylation of **17** with TBAF gave **18** (96 %) and subsequent Ley oxidation[18] led to aldehyde **19** (87 %) in seven steps and 49 % overall yield from **15**.

With the two key fragments in hand, we next turned to the critical, convergent coupling step. We were pleased to observe that **14** and **19** participated in an aldol addition reaction with Bu_2BOTf/Hünig's base to give β-hydroxy ketone **20** in excellent yield (80 %) as a single diastereomer (by ^1H NMR) possessing the requisite 1,5-*anti* configuration (Scheme 4).[19] Unfortunately, **20** failed to undergo reduction under Tishchenko conditions.[20] Alternatively, *anti* diol **21** was obtained from **20** by using $Me_4NBH(OAc)_3$[21] (97 %, d.r. > 95:5 by ^1H NMR). Cleavage of the C17 benzoate (K_2CO_3, MeOH) gave access to key intermediate **22** (92 %).

The second tetrahydropyran ring was installed by an electrophile-mediated cyclization of the C11 hydroxy group onto the C=C double bond.[22] A number of electrophiles, including I_2, IBr,[23] and $Hg(OAc)_2$ were screened, albeit all gave disappointing levels of diastereoselectivity (1:1). We subsequently decided to investigate selenium electrophiles, and promising results with phenylselenyl chloride (d.r. 3:1, *anti*:*syn*) prompted us to examine bulkier, substituted phenylselenyl halides.[24] In this respect, 2,4,6-triisopropylphenylselenyl bromide was the reagent of choice: Indeed **22** underwent clean cyclization in CH_2Cl_2 to the desired 2,6-*trans*-substituted tetrahydropyran **23** (74 %, d.r. 88:12 by ^1H NMR). To the best of our knowledge, the stereoselective formation of 2,6-substituted *trans* tetrahydropyrans mediated by 2,4,6-triisopropylphenylselenyl bromide is unprecedented. Reductive deselenylation of **23** to **24** (80 %) was achieved under tin-free conditions with the silylated 1,4-cyclohexadiene reagent recently developed by Studer and Amrein.[25] Following ester hydrolysis with TMSOK, *seco* acid **25** was obtained. Our objective at this point in the synthesis was to differentiate the two secondary hydroxy groups at C9 and C17 through a regioselective macrolactonization reaction.[26] To our surprise, however, lactonization of the *seco* acid under the standard Yamaguchi conditions with various solvents (benzene, toluene, xylene, THF) failed to give any product. Instead a complex mixture of oligomers was obtained.

In earlier feasibility studies in our laboratory, we had observed that macrolactonization proceeded smoothly under Yamaguchi conditions from the precursor incorporating a C9 methyl ether.[27] We hypothesized that the structure possessing a hydrogen-bonded network involving the C9 hydroxy group preorganizes the C7–C11 backbone in an arrangement that places the C9 oxygen atom between the tetrahydropyrans thus precluding cyclization.[28] Consequently, we speculated that conducting the lactonization in a polar solvent able to disrupt hydrogen bonds would help the system adopt the necessary conformation for cyclization. Indeed, the use of DMF as solvent cleanly leads to macrocycle **26**, which, after O-methylation of the C9 alcohol with Me_3OBF_4[29] in the

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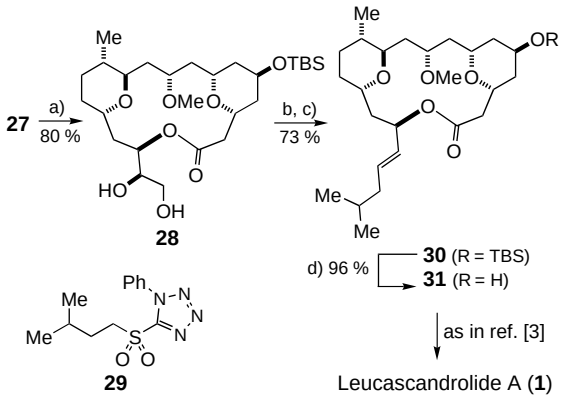
presence of proton sponge, furnished **27** (49% over 3 steps from **24**).

Hydrolysis of the acetonide present in **27** gave diol **28** (80%) without cleavage of the silyl ether; subsequent oxidative cleavage of the glycol furnished the corresponding aldehyde, setting the stage for the introduction of the C17 side chain (Scheme 5). Towards this aim, we used the Kocienski modification of the Julia–Lythgoe olefination[30] with sulfone



Scheme 5. a) AcOH/THF/H_2O 2:1:1, 45°C, 5 h, 80%; b) $Pb(OAc)_4$, EtOAc, 0°C, 15 min; c) **29**, KHMDS, DME, −78°C→0°C, 73% (2 steps) (E:Z > 95:5); d) TBAF, THF, 0°C→RT, 7 h, 96%. DME = 1,2-dimethoxy ethane, KHMDS = potassium hexamethyldisilazide.

29[31] to provide olefin (E)-**30** as a single isomer (by ^{1}H NMR) (73% over 2 steps). Deprotection of the secondary silyl ether furnished macrolide **31**, which was identical in all respects (^{1}H NMR, ^{13}C NMR, IR, HRMS, $[\alpha]_D$) with the intermediate reported previously.[1,3,4] With a formal synthesis of **1** in hand, we proceeded to complete the total synthesis following the Leighton strategy to give fully synthetic leucascandrolide A.[3]

In summary, we have reported an expedient, stereocontrolled total synthesis of leucascandrolide A (23 steps longest linear sequence, 2% overall yield). The salient methodological features of the approach include: 1) the use of a reagent-controlled zinc alkynilide addition to isopropylidene glyceraldehyde; 2) catalytic, enantioselective dienolate aldol addition to crotonaldehyde; 3) the use of a selenium-mediated cylization reaction for the formation of a *trans*-substituted tetrahydropyran. Moreover, interesting observations concerning hydrogen-bonding effects and conformational flexibility were made in the context of the macrocyclization reaction that may be applicable to other systems.

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[1] M. D'Ambrosio, A. Guerriero, C. Debitus, F. Pietra, *Helv. Chim. Acta* **1996**, *79*, 51–60.

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

[3] K. R. Hornberger, C. L. Hamblett, J. L. Leighton, *J. Am. Chem. Soc.* **2000**, *122*, 12894–12895.

[4] D. J. Kopecky, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2001**, *123*, 8420–8421.

[5] M. T. Crimmins, C. A. Carroll, B. W. King, *Org. Lett.* **2000**, *2*, 597–599.

[6] S. A. Kozmin, *Org. Lett.* **2001**, *3*, 755–758.

[7] P. Wipf, T. H. Graham, *J. Org. Chem.* **2001**, *66*, 3242–3245.

[8] a) D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807; b) E. El-Sayed, N. K. Anand, E. M. Carreira, *Org. Lett.* **2001**, *3*, 3017–3020; c) N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688; d) D. Boyall, F. López, H. Sasaki, D. Frantz, E. M. Carreira, *Org. Lett.* **2000**, *2*, 4233–4236.

[9] a) J. Krüger, E. M. Carreira, *J. Am. Chem. Soc.* **1998**, *120*, 837–838; b) B. L. Pagenkopf, J. Krüger, A. Stojanovic, E. M. Carreira, *Angew. Chem.* **1998**, *110*, 3312–3314; *Angew. Chem. Int. Ed.* **1998**, *37*, 3124–3126; ; c) R. A. Singer, E. M. Carreira, *J. Am. Chem. Soc.* **1995**, *117*, 12360–12361.

[10] K.- M. Chen, K. G. Gunderson, G. E. Hardtmann, K. Prasad, O. Repic, M. J. Shapiro, *Chem. Lett.* **1987**, 1923–1926.

[11] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

[12] D. A. Evans, J. A. Gauchet-Prunet, *J. Org. Chem.* **1993**, *58*, 2446–2453.

[13] a) E. Keinan, K. K. Seth, R. Lamed, *J. Am. Chem. Soc.* **1986**, *108*, 3474–3480; b) J. Tsuji, *Synthesis* **1984**, 369–384.

[14] J. W. Bode, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 3611–3612.

[15] S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, 521–522.

[16] (R)-isopropylidene glyceraldehyde was prepared from D-mannitol: C. R. Schmid, J. D. Bryant, M. Dowlatzedah, J. L. Phillips, D. E. Prather, R. D. Schantz, N. L. Sear, C. S. Vianco, *J. Org. Chem.* **1991**, *56*, 4056–4058.

[17] Additions to **5** are known to be fairly nonselective: S. H. Kang, W. J. Kim, *Tetrahedron Lett.* **1989**, *30*, 5915–5918.

[18] W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc. Chem. Commun.* **1987**, 1625–1627.

[19] a) I. Paterson, K. R. Gibson, R. M. Oballa, *Tetrahedron Lett.* **1996**, *37*, 8585–8588; b) I. Paterson, R. M. Oballa, R. D. Norcross, *Tetrahedron Lett.* **1996**, *37*, 8581–8584; c) D. A. Evans, P. J. Coleman, B. Côté, *J. Org. Chem.* **1997**, *62*, 788–789.

[20] D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.

[21] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *120*, 3560–3578.

[22] For a review, see: a) M. Frederickson, R. Grigg, *Org. Prep. Proced. Int.* **1997**, 29, 35–62; b) M. Frederickson, R. Grigg, *Org. Prep. Proced. Int.* **1997**, 29, 63–115.

[23] J. J.-W. Duan, A. B. Smith III, *J. Org. Chem.* **1993**, *58*, 3703–3711.

[24] B. H. Lipshutz, T. Gross, *J. Org. Chem.* **1995**, *60*, 3572–3573.

[25] A. Studer, S. Amrein, *Angew. Chem.* **2000**, *39*, 3196–3198; *Angew. Chem. Int. Ed.* **2000**, *39*, 3080–3082.

[26] L. Mandolini, *J. Am. Chem. Soc.* **1978**, *100*, 550–554.

[27] The groups of Leighton and Rychnovsky have reported similar macrolactonizations with C9 methyl ether derivatives.

[28] Molecular mechanics calculations for the macrolide portion of Leucascandrolide A reveal that the C9 oxygen atom resides peripherally: see ref. [1].

[29] R. E. Ireland, L. Liu, T. D. Roper, J. L. Gleason, *Tetrahedron* **1997**, *53*, 13257–13284.

[30] a) P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett* **1998**, 26–28; b) J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Tetrahedron Lett.* **1991**, *32*, 1175–1178.

[31] Sulfone **29** was prepared by Mitsunobu reaction followed by oxidation with oxone.

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