Catalytic Asymmetric Synthesis of Macrocyclic (*E*)-Allylic Alcohols from ω-Alkynals via Intramolecular 1-Alkenylzinc/Aldehyde Additions

Wolfgang Oppolzer,† Rumen N. Radinov,‡ and Emad El-Sayed*,§

Département de Chimie Organique, Université de Genève, CH-1211 Genève 4, Switzerland

emadel-sayed@carbogen.com

Received March 28, 2000 (Revised Manuscript Received March 27, 2001)

The ω-alkynals yielded macrocyclic (*S*)-allylic alcohols in a one-pot reaction sequence involving alkyne monohydroboration, boron to zinc transmetalation, and ((+)-DAIB)-catalyzed enantioselective intramolecular ring closure to the aldehyde function. A general study of this macrocyclization methodology is presented with respect to ligand type, size, and nature of the formed rings.

Introduction

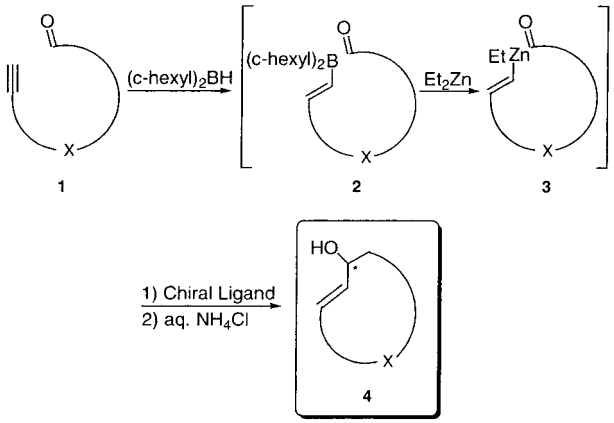
Asymmetric catalytic processes have found increasing application in the synthesis of complex chiral molecules and natural products.[1] Rate acceleration of reactions apart, the use of chiral catalysts benefits the transfer and multiplication of chirality. A prime example, and often a test case for new chiral ligands, is the catalytic enantioselective addition of dialkylzinc reagents to aldehydes.[2] Oppolzer and Radinov have broadened the scope of applications of this methodology to include the catalytic enantioselective addition of alkenylzinc reagents to aliphatic as well as aromatic aldehydes.[3] Intramolecular addition of alkenylzinc reagents to the aldehyde function has subsequently been applied to the synthesis of two macrocyclic natural products, (*R*)-(−)-muscone[4a] and (+)-aspicilin.[4b]

Herein, we report a systematic study of this macrocyclization methodology with respect to (i) reproducibility, (ii) ligand type, and (iii) size and nature of the macrocycle.

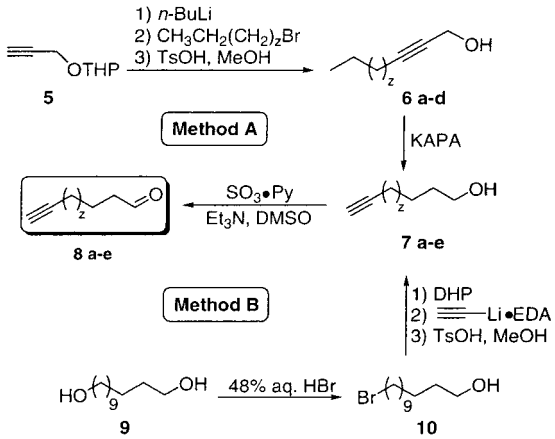
Results and Discussion

Our general approach to macrocyclic (*E*)-allylic alcohols is outlined in Scheme 1.[4] Selective monohydroboration of readily available ω-alkynals **1** (X = CH_2 or an ester group as part of the tether), boron/zinc-transmetalation (**2** → **3**) and chiral ligand-catalyzed intramolecular addition of the alkenylzinc intermediate **3** to the aldehyde group offers an efficient approach to chiral allyl alcohol-containing carbocycles and macrolides **4**.

Scheme 1. General Approach to Macrocyclic (*E*)-allylic Alcohols



Scheme 2. Synthesis of Carbocycle Precursors



As indicated in Scheme 2, lithiation of the commercially available THP-protected propargyl alcohol **5** followed by reaction with alkyl bromides,[5] base-induced alkyne isomerization of the resulting 2-alkyn-1-ols **6**,[6] and finally Parikh−Doering oxidation[7] afforded ω-alkynals **8**

† Deceased on March 15, 1996.

‡ Present address: Hoffmann-LaRoche, Inc., Chemical Synthesis Department, 66/208, 340 Kingsland Street, Nutley, NJ 07110-1199.

§ Present address: CarboGen Laboratories (Neuland) AG, Neulandweg 5, CH-5502 Hunzenschwil, Switzerland.

(1) (a) Noyori, R. In *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) Seyden-Penne, J. In *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995.

(2) (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (c) Erdik, E. In *Organozinc Reagents in Organic Synthesis*; CRC: New York, 1996; pp 107−206.

(3) (a) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1988**, *29*, 5645. (b) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777. (c) Oppolzer, W.; Radinov, R. N. *Helv. Chem. Acta* **1992**, *75*, 170.

(4) (a) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593. (b) Oppolzer, W.; Radinov, R. N.; De Brabander, J. *Tetrahedron Lett.* **1995**, *36*, 2607.

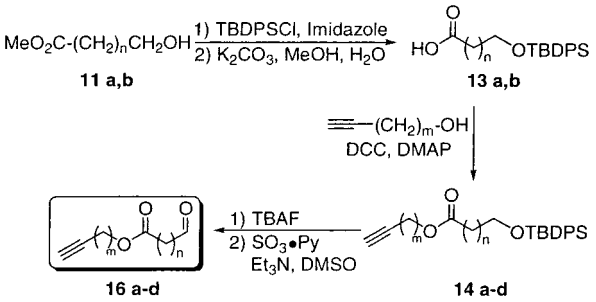
(5) (a) Schwarz, M.; Waters, R. M. *Synthesis* **1972**, 567. (b) Mitra, R. B.; Reddy, G. B. *Synthesis* **1989**, 694.

(6) KAPA = Potassium 3-aminopropylamide. Abrams, S. R. *Can. J. Chem.* **1984**, *62*, 1333.

(7) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

10.1021/jo000463n CCC: $20.00
Published on Web 06/20/2001

Scheme 3. Synthesis of Macrolide Precursors



Scheme 4. Synthesis of Macrolide Precursors Having the Opposite Disposition of the Ester Function

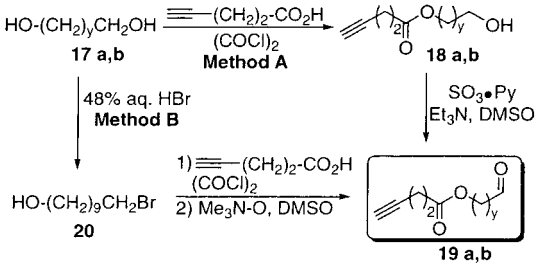


Table 1. Synthesis of ω-Alkynals 8

entry	*z*	chain length	yield (%)[a] 6	7	10	7	8[b]
a	8	13	85	70	–	–	76 (**A**)
b	9	14	–	–	54	72	87 (**B**)
c	10	15	77	76	–	–	81 (**A**)
d	13	18	79	82	–	–	52 (**A**)
e	16	21	68	77	–	–	72 (**A**)

[a] Yields refer to isolated and purified compounds. [b] The method used for the synthesis is indicated in parentheses.

in good yields. Alternatively, **8** was obtained via conversion of the α,ω-diol **9** into ω-bromoalkanol **10**,[8] followed by O-protection, alkylation with the lithium acetylide·EDA complex,[9] deprotection, and finally oxidation.

Ester alcohols **11**, accessed via esterification of ϵ-caprolactone,[10] or via a selective reduction of monomethyl azelate,[11] were O-protected with *tert*-butyldiphenylchlorosilane (TBDPSCl) as depicted in Scheme 3. This was followed by methyl ester hydrolysis, esterification with the corresponding ω-alkynols as well as **7**, tetrabutylammonium fluoride (TBAF) silyl ether deprotection, and subsequent oxidation to produce **16**.

The ω-alkynals **19** having the differently connected ester function in the tether were accessed via esterification of 4-pentynoic acid with the corresponding diols **17** followed by oxidation of the resulting ω-alkynols **18**, as illustrated in Scheme 4. Alternatively, esterification with bromo alcohol **20** followed by anhydrous trimethylamine *N*-oxide oxidation[12] of the resulting ω-bromoalkyne yielded the ω-alkynal **19**. Tables 1−3 summarize the results obtained in the syntheses of ω-alkynals **8**, **16**, and **19** respectively. ω-Alkynal **8c** was selected to elaborate

Table 2. Synthesis of ω-Alkynals 16

entry	*n*	*m*	chain length	yield (%)[a] 11	12	13	14	15	16
a	4	4	12	53	92	95	65	93	83
b	7	4	15	76	88	99	67	91	83
c	4	8	16	–	–	–	65	97	90
d	4	12	20	–	–	–	70	96	75

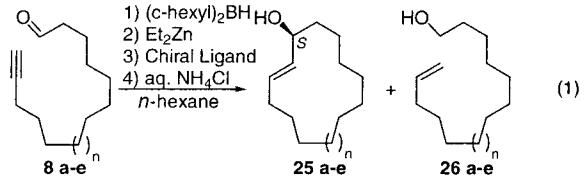
[a] Yields refer to isolated and purified compounds.

Table 3. Synthesis of ω-Alkynals 19

entry	*x*	*y*	chain length	yield (%)[a] method A 18	method A 19	method B 20	method B 19
a	2	9	15	56	76	81	60
b	2	10	16	51	71	–	–

[a] Yields refer to isolated and purified compounds.

optimum conditions for the transmetalation/intramolecular alkenylzinc-aldehyde addition (eq 1). Thus reaction



(1)

of **8c** with freshly prepared dicyclohexylborane dimethyl sulfide complex at −20 °C to 0 °C led to a selective monohydroboration of the alkyne function. This was followed by dilution and slow addition (over 4 h) to 2 mol % **21**/Et_2Zn mixture at 0 °C. Workup with aq NH_4Cl provided the expected (*S*)-allylic alcohol **25c**.

Our early attempts to effect the macrocyclization by the original procedure[4a] using the (+)-DAIB ligand **21** (1 mol %) afforded the 15-membered macrocycle **25c** in only 36−39% yield (84% ee) together with 7% of the open chain reduced product **26c**. Yields and selectivities were improved by (i) careful drying (over $LiAlH_4$) and degassing of *n*-hexane (HPLC-grade), (ii) drying (over CaH_2) and degassing of cyclohexene, (iii) distilling **21** prior to its use, (iv) weighing the chiral ligands in a glovebox and preparing stock solutions in dry degassed *n*-hexane for more precise and practical manipulation, and (v) distilling Et_2Zn under high vacuum (20 °C/0.2 mmHg).

Carring out the reaction at 0.3−0.4 M dilution using (1*S*)-(+)-3-*exo*-(dimethylamino)isoborneol ((+)-DAIB) (**21**)[13] as chiral ligand resulted in product polymerization rather than cyclization (Table 4, entry 1). At higher dilution, macrocyclization was successful and after some experimentation, optimal conditions were found using dilution values of 0.05 M for both hydroborated intermediate and the Et_2Zn/(+)-DAIB mixture (Table 4, entries 2−5).

Using the optimized procedure for the macrocyclization of ω-alkynal **8c** (eq 1), a number of chiral ligands were tested in the reaction: (+)-DAIB **21**,[13] (*S*,*S*)-Zn-(STDMBA)$_2$ **22**,[14] (1*R*)-**23**,[15] and (1*S*)-**24**.[15]

(8) Kang, S.-K.; Kim, W.-S.; Moon, B.-H. *Synthesis* **1985**, 1161.
(9) EDA = Ethylenediamine. Rossi, R. *Synthesis* **1981**, 359.
(10) Bosone, E.; Farina, P.; Guazzi, G.; Innocenti, S.; Marotta, V. *Synthesis* **1983**, 942.
(11) Kanth, J. V. B.; Periasamy, M. *J. Org. Chem.* **1991**, *56*, 5964.
(12) Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1990**, *31*, 4825.
(13) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.
(14) Rijnberg, E.; Jastrzebski, J. T. B. H.; Janssen, M. D.; Boersma, J.; van Koten, G. *Tetrahedron Lett.* **1994**, *35*, 6521
(15) (a) Bernardinelli, G.; Fernandez, D.; Gosmini, R.; Meier, P.; Ripa, A.; Schüpfer, P.; Treptow, B.; Kündig, E. P. *Chirality* **2000**, *12*, 529. (b) See also Kündig, E. P.; Meier, P. *Helv. Chem. Acta* **1999**, *82*, 1360.

Table 4. Concentration Dependence of the Macrocyclization Step[a]

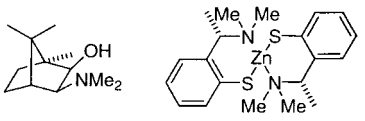
entry	(+)-DAIB (mol %)	hydroborated species, M	Et_2Zn/DAIB mixture, M	yield (%)[b]
1	2	0.33	0.38	polymer
2	5	0.03	0.02	67
3	0	0.03	0.02	traces
4	1	0.05	0.05	73[c]
5	2	0.01	0.01	16[d]

[a] All reactions were run on a 1 mmol scale of **8c** at 0 °C. [b] Yields refer to isolated and purified products. [c] This reaction refers to that obtained in ref 4a. [d] A mixture of products was obtained including **25c**, 14-pentadecen-1-ol **26c**, and 14-pentadecenal in 16%, 13%, and 14%, respectively.

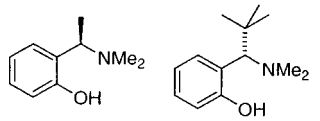
Table 5. Effect of Ligand Type and Quantity on Yield and Selectivity[a]

entry	ligand[b]	temp,[c] °C	yield (%)[d] **25c**	yield (%)[d] **26c**	ee (%)[e] of **25c**
1	**21** (1)	0	53	3	87
2	**21** (2)	0	60	3	88
3	**21** (3)	0	61	4	90
4	**21** (4)	0	66	4	88
5	**22** (0.5)	0	60	4	65
6	**22** (0.5)	−10	57	4	62
7	**22** (2)	−30	53	3	62
8[f]	(*R*)-**23** (2)	0	19	3	27
9[g]	(*S*)-**24** (2)	0	23	4	33

[a] All reactions were run on a 1 mmol scale of **8c** in *n*-hexane. [b] Values in parentheses refer to the precatalyst load expressed in mol %. [c] Temperature refers to that used during the transmetalation and intramolecular addition steps. [d] Yields are based on isolated and purified compounds and corrected by ^{1}H NMR. [e] Enantiomeric excess (ee) determined by ^{19}F NMR of the (1*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate.[16] [f] This reaction afforded the opposite absolute stereochemistry (cf. eq 1). [g] This reaction was run on 0.5 mmol scale of **8c**.



21 (+)-DAIB **22** (*S,S*)-Zn(STDMBA)$_2$



(*R*)-**23** (*S*)-**24**

As seen by the results of Table 5, by increasing the load of **21**, higher yields were progressively obtained while selectivity[16] remained practically constant. This indicates the independence of the aldehyde diastereofacial discrimination vis-à-vis ligand load. On the other hand, zinc complex **22** and aminophenols **23** and **24** afforded **25c** in moderate and low selectivities, respectively (Table 5, entries 5−9).

Application of this macrocyclization protocol to ω-alkynals **8** afforded the expected (*S*)-allylic alcohols **25** in 88−91% enantiomeric excess (eq 1, Table 6).

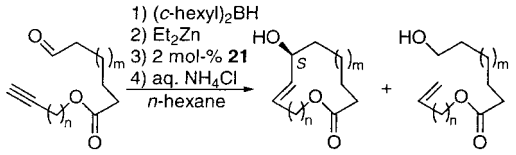
Not surprisingly, 13- and 14-membered rings **25a** and **25b** were obtained in only low yields, reflecting the strain due to an endocyclic (*E*)-double bond. The larger, 15- and 18-membered rings **25c** and **25d** were isolated in yields of about 60%. Due to its increased ring size and low solubility, the 21-membered ring **25e** was isolated in only 43% yield.

Table 6. Macrocyclization of 8 to Carbocyclics 25[a]

entry	*n*	ring size	yield (%)[b] **25**	yield (%)[b] **26**	ee (%)[c] of **25**
a	1	13	20	9	90
b	2	14	35	7	91
c	3	15	60	3	88
d	6	18	61	7	91
e	9	21	43	8	88

[a] All reactions were run on a 1 mmol scale of **8** in *n*-hexane at 0 °C in the presence of 2 mol % **21**. [b] Yields are based on isolated and purified compounds and corrected by ^{1}H NMR. [c] Enantiomeric excess (ee) determined by ^{19}F NMR of the corresponding (1*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate esters.[16]

Table 7. Macrocyclization of 16 to Macrolides 27[a]



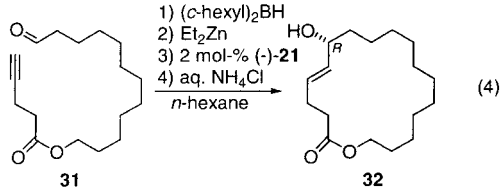
16 a-d **27 a-d** **28 a-d**

entry	*n*	*m*	ring size	yield (%)[b] **27**	yield (%)[b] **28**	ee (%)[c] of **27**
a	4	1	13	14	9	71
b	4	4	16	65	8	89
c	8	1	17	45	3	90
d	12	1	21	48	4	90

[a] All reactions were run on a 1 mmol scale of **16** in *n*-hexane at 0 °C in the presence of 2 mol % **21**. [b] Yields are based on isolated and purified compounds and corrected by ^{1}H NMR. [c] Enantiomeric excess (ee) determined by ^{19}F NMR of the corresponding (1*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate esters.[16]

Alkynal esters **19**, having the alternative disposition of the ester oxygen and carbonyl group, also provide macrocyclic (*S*)-allyl alcohols **29** by standard ring closure of 4-pentynoyl esters **19** (eq 3, Table 8).

Inspection of Tables 6, 7, and 8 reveals the fact that unlike carbocyclic (*S*)-allylic alcohols **25**, macrolides **27** and **29** are produced in moderate yields, reaching a maximum of 65% with the 16-membered rings **27b** and **29a**. This observation is in line with previously reported ring closure of ω-alkynal **31** yielding the corresponding 18-membered macrolide **32** in 25−52% and in 79% ee as outlined in eq 4.[4b]

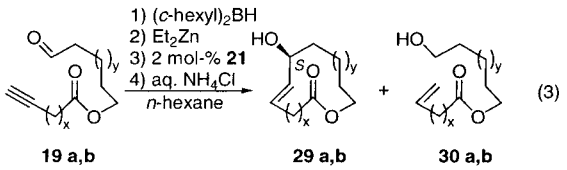


31 **32**

We noted that aldehyde π-face discrimination is constant at about 90% ee. Only in cases (e.g., **27a**) where

(16) Determined via ^{19}F NMR of the corresponding Mosher esters: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Table 8. Macrocyclization of 19 to Macrolides 29[a]



19 a,b **29 a,b** **30 a,b**

entry	*x*	*y*	ring size	yield (%)[b] **29**	yield (%)[b] **30**	ee (%)[c] of **29**
a	2	6	16	65	8	90
b	2	7	17	44	6	73

[a] All reactions were run on a 1 mmol-scale of **19** in *n*-hexane at 0 °C in the presence of 2 mol % **21**. [b] Yields are based on isolated and purified compounds and corrected by ^{1}H NMR. [c] Enantiomeric excess (ee) determined by ^{19}F NMR of the corresponding (1*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate esters.[16]

the ester and alkenylzinc units are proximal in the cyclization precursor do we find lower selectivities (e.g., Table 7, entry a). In the case of **29b** and **32**, the chain length contributes to the structural mobility which, unfortunately, leads to higher degrees of freedom in the transition state[4a] and, consequently, to lower ee's.

Conclusion

We conclude that asymmetrically catalyzed macrocyclizations offer an efficient approach to naturally occurring chiral carbocycles and macrolides as exemplified by a synthesis of (*R*)-(−)-muscone[4a] and (+)-aspicilin.[4b] The methodology produces low to moderate yields of 13- and 14-membered carbocycles, respectively, while yields level off at 60% for 15-membered and larger carbocycles. Macrolides are generally produced in moderate yields and reach a maximum of 65% in the case of 16-membered rings regardless of the ester group disposition within the tether between the alkyne and aldehyde reactive sites. Proximity of the ester and alkenylzinc units in the cyclization precursor may diminish the reaction yield. Enantiomeric excess remains constant at about 90% albeit that ring size affects selectivity in some cases.

Experimental Section

General. All solvent distillations and glovebox manipulations were carried under a dry nitrogen atmosphere. All reactions and reagent distillations were carried under an argon atmosphere with magnetic stirring. "Workup" denotes extraction with ether, drying (Na_2SO_4 or $MgSO_4$), and evaporation (rotary evaporator). Column flash chromatography (FC): SiO_2 (Merck 9385). Solvents were dried by distillation from drying agents as follows: ether (Na/benzophenone), dichloromethane (CaH_2), *n*-hexane ($LiAlH_4$), HMPA (BaO).

General Method for the Synthesis of 2-Alkyn-1-ols 6. A solution of tetrahydro-2-(2-propynyloxy)-2*H*-pyran **5** (2.81 mL, 20 mmol) in dry THF (20 mL) was cooled to 0 °C in an ice bath and treated with 1.6 M solution of *n*-butyllithium in hexane (5.5 mL, 23 mmol). Thereafter, 1-bromoalkane (23 mmol) in dry distilled HMPA (40 mL) was added at 0 °C and the resulting reaction mixture stirred 1.5 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution followed by extraction with pentane. The combined organic extracts were washed with water and dried ($MgSO_4$). After concentration, the residual oil was dissolved in methanol (50 mL), and 4-toluenesulfonic acid monohydrate (2 g, 10.5 mmol) was added at room temperature. The reaction mixture was stirred at room-temperature overnight, poured into ice-cold water, extracted with ether, dried ($MgSO_4$), and concentrated and the residue flash chromatographed (SiO_2; *n*-hexane:ether = 3/1) to give the product (see Table 1).

General Method for the Base-Induced Alkyne Isomerization 7. Lithium wire (709 mg, 102.2 mmol) was cut into fine pieces in dry *n*-hexane and mixed with dry distilled 1,3-diaminopropane (50 mL). The mixture was stirred at 75 °C (bath temperature) overnight to yield a milky white reaction mixture. After cooling to room temperature, potassium *tert*-butoxide (6 g, 54 mmol) was added in one portion. The pale yellow colored mixture was stirred at room temperature for 15 min before addition of **6** (14 mmol) in one portion. The now pale brown reaction mixture was stirred at room temperature for 5 h. The reaction mixture was quenched by pouring into ice-cold water followed by extraction with ether and drying ($MgSO_4$). After concentration, the yellow solid residue was flash chromatographed (SiO_2; *n*-hexane:ether = 2/1) to give the product (see Table 1).

General Procedure for the Parikh−Doering Oxidation of 7. Triethylamine (14 mL, 100.44 mmol) was added to a stirred solution of **7** (10 mmol) in dry CH_2Cl_2 (9 mL) at room temperature and the resulting mixture treated with a solution of sulfur trioxide pyridine complex (5.6 g, 35.18 mmol) in DMSO (35 mL) at room temperature under a dry argon atmosphere. The reaction mixture was stirred for 2−5 h at room temperature and then quenched by pouring into water and extracted with ether. The combined ether extracts were washed with 0.2 M HCl solution, water, and brine. After drying ($MgSO_4$) and concentration, the residual yellow oil was flash chromatographed (SiO_2; *n*-pentane:ether = 10/1) to afford the product (see Table 1).

ω-((1,1-Dimethylethyl)diphenylsilyloxy)carboxylic Acid ω-Alkynyl Ester 14. To a solution of **13** (15 mmol) in dry ether (75 mL) was added 5-hexynol, or **7** (16.5 mmol), followed by DMAP (0.18 g, 1.47 mmol) and DCC (3.4 g, 16.5 mmol) at room temperature. The reaction mixture was stirred overnight at room temperature and then filtered and the precipitate washed with ether. The combined filtrates were concentrated, and the resulting oily residue was flash chromatographed (SiO_2; *n*-hexane:ether = 15/1), affording the ester (see Table 2).

ω-Hydroxycarboxylic Acid ω-Alkynyl Ester 15. A solution of **14** (8 mmol) in dry THF (2 mL) was treated with TBAF (1 M solution in THF, 18 mL, 18 mmol) with stirring at room temperature. The resulting reaction mixture was stirred for 1.5 h at room temperature, diluted with ether, washed with water, brine, dried ($MgSO_4$), concentrated, and flash chromatographed (SiO_2; *n*-hexane:ether = 2/3) to afford the free alcohol (see Table 2).

4-Pentynoic Acid ω-Hydroxyalkyl Ester 18. A solution of 4-pentynoic acid (0.5 g, 5.1 mmol) in dry CH_2Cl_2 (5 mL) was treated with dry DMF (20 mL, 0.26 mmol) and oxalyl chloride (0.55 mL, 6.4 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h before distilling off CH_2Cl_2. The remaining residue was dissolved in dry THF (2.5 mL). Separately, α,ω-alkanediol **17** (7.63 mmol) was added to a suspension of NaH (60% in mineral oil, 0.31 g, 7.75 mmol) in dry THF (10 mL) and then refluxed overnight. After cooling to room temperature, the acid chloride solution was added dropwise to the diol/NaH reaction mixture during 3 h. After complete addition, the reaction mixture was stirred at room temperature for further 2 h before dilution with ether and wash with 10% aq K_2CO_3 solution, water, and brine. After drying ($MgSO_4$) and flash chromatography (SiO_2; *n*-hexane:ether = 1/2), the pure product was obtained (see Table 3).

General Macrocyclization Procedure. A solution of borane−dimethyl sulfide complex (100 μL, 1 mmol) in dry degassed *n*-hexane (1 mL) was treated by dropwise addition of dry degassed cyclohexene (205 μL, 2 mmol) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C where a white suspension of dicyclohexylboranedimethyl sulfide complex was formed. A solution of ω-alkynal **8**, **16**, or **19** (1 mmol) in dry degassed *n*-hexane (4 mL) was dropwised into the white suspension at −20 °C during 1−2 min. The reaction mixture was then allowed to reach 0 °C during 30 min and stirred at 0 °C for 1 h where a clear colorless reaction mixture was obtained. Separately, diethylzinc (155 μL, 1.5 mmol) in dry

degassed *n*-hexane (3 mL) was treated at 0 °C with a solution of (1*S*)-(+)-3-*exo*-(dimethylamino)isoborneol **21** (0.02 mmol) and the resulting mixture diluted with dry degassed *n*-hexane (27 mL) to 0.05 M at 0 °C during 20 min using a syringe pump. The borane derivative reaction mixture was then diluted with dry degassed *n*-hexane (15 mL) to 0.05 M at 0 °C then was added dropwise to Et_2Zn/(+)-DAIB mixture via syringe pump at 0 °C during 4 h with vigorous stirring. After complete addition, the reaction mixture was stirred for an additional period of 30 min at 0 °C before quenching with saturated aqueous NH_4Cl solution and extraction with ether, followed by drying ($MgSO_4$). After concentration, the colorless oily residue was flash chromatographed (SiO_2; *n*-hexane:ether = 5/2 for carbocycles **25** and 1/1 for macrolides **27** and **29**), affording the macrocycles as in Tables 6, 7, and 8.

Acknowledgment. Financial support of this work by Swiss National Science Foundation (CHIRAL-2) and Givaudan-Roure AG., Dübendorf, is gratefully acknowledged. We thank Profs. E. Peter Kündig and Jef De Brabander for discussions and help with the manuscript. We thank Mr. J. P. Saulnier, and Mr. A. Pinto and Mrs. D. Klink, for NMR and MS measurements, respectively. Profs. E. Peter Kündig and Gerard van Koten are gratefully acknowledged for their generous donation of precatalysts **23**, **24**, and **22**, respectively.

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra of all compounds and copies of ^{19}F NMR spectra of the Mosher esters of the corresponding macrocycles. Characterization data for compounds **6a**, **6c**, **6d**, **6e**, **7a**, **7b**, **7c**, **7d**, **7e**, **8a**, **8b**, **8c**, **8d**, **8e**, **14a**, **14b**, **14c**, **14d**, **15a**, **15b**, **15c**, **15d**, **16a**, **16b**, **16c**, **16d**, **18a**, **18b**, **19a**, **19b**, **25a**, **25b**, **25c**, **25d**, **25e**, **27a**, **27b**, **27c**, **27d**, **29a**, **29b**. Synthetic procedures for compounds **11b**, **12a**, **12b**, **13a**, **13b**, **20a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000463N