Enantioselective Total Synthesis of Gracilins B and C Using Catalytic Asymmetric Diels–Alder Methodology

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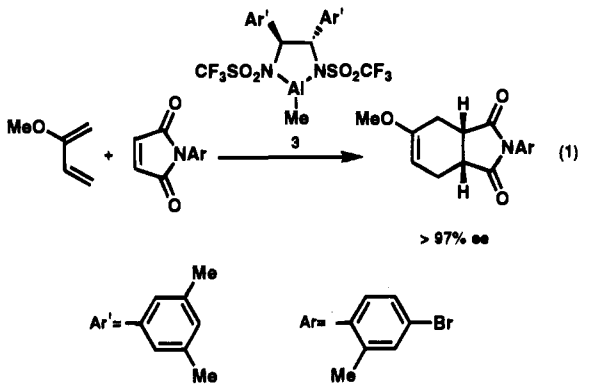
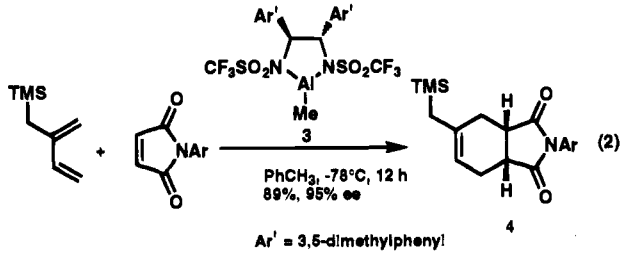
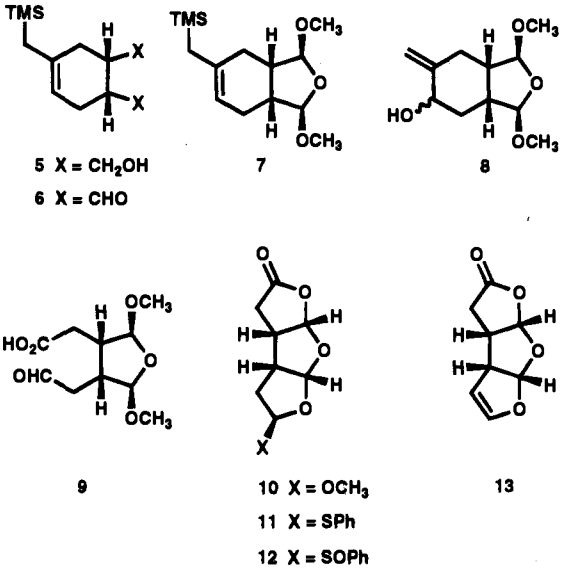
The synthesis of structurally complex natural products has been greatly enhanced by the advent of new enantioselective reactions which literally have provided a totally new set of powerful tools for molecular construction. We recently have reported a new catalytic Diels–Alder reaction of 2-methoxybutadiene with *N*-arylmaleiimides which proceeds with remarkably high enantioselectivity as exemplified by eq 1.[1-3] We describe herein the application of this discovery to a challenging synthetic problem, the first synthesis of the biosynthetically and structurally unusual marine natural products gracilin B (**1**) and C (**2**) from a common intermediate.[4]



The correct chirality and all the carbon atoms of the trioxacyclic ring system of the gracilins were established in the initial Diels–Alder step. Reaction of 2-((trimethylsilyl)methyl)-butadiene[5] with *N*-(2-*tert*-butylphenyl)maleiimide[1] in the presence of 20 mol % of catalyst **3**[1] in toluene solution at −78 °C for 12 h produced adduct **4** in 89% yield and with 95% ee;[6] recrystallization from hexane afforded enantiomerically pure **4**, mp 114–115 °C; $[\alpha]^{23}_D$ −35.2° (c = 1, $CHCl_3$) (eq 2). The



absolute configuration of **4** was determined by S_E2' protonation–desilylation to the corresponding methylenecyclohexane derivative (BF_3–HOAc) and oxidative cleavage ($NaIO_4$–OsO_4 aqueous *t*-BuOH) to the corresponding cyclohexanone $[\alpha]^{23}_D$ −35.5° (c = 3, CH_2Cl_2), which was identical with the known chiral ketone from acid hydrolysis of the Diels–Alder adduct of 2-methoxybutadiene and *N*-(2-*tert*-butylphenyl)maleiimide in the presence of catalyst **3**.[1,7] Adduct **4** was transformed to the diol **5** by a three-step sequence consisting of (1) reduction to a 1:1 mixture of position-isomeric hydroxy amides (from non-position-selective imide carbonyl reduction) using 6.8 equiv of $NaBH_4$ in 6:1 *i*-PrOH–H_2O at 23 °C for 16 h (100% yield); (2) lactonization by heating with 1.8:1 Et_3N–HOAc at 80 °C for 96 h (85% yield of a 1:1 mixture of γ-lactones); and (3) reduction to a single diol (**5**, 95% yield) with 1 equiv of $LiAlH_4$ in ether at 23 °C for 15 h. Swern oxidation of diol **5** (2.3 equiv of oxalyl chloride and 3.8 equiv of Me_2SO in CH_2Cl_2 at −78 °C followed by excess Et_3N) provided dialdehyde **6**, which was treated sequentially with excess CH_3OH in CH_2Cl_2 at −78 °C for 10 min and then with excess $(MeO)_2SO_2$ and NaOAc at 0 °C for 0.5 h to give the cyclic bis-acetal **7**, $[\alpha]^{23}_D$ −14.7° (c = 6, $CHCl_3$), in 70% overall yield from **5**. Exposure of **7** to 1.2 equiv of dimethyldioxirane[8] in Me_2CO at 0 °C for 15 min produced a mixture of diastereomeric epoxides, which upon reaction with 1.1 equiv of *n*-Bu_4NF in THF at 0 °C for 40 min was converted to a diastereomeric mixture (*ca.* 2:1) of allylic alcohols **8** (87% from **7**). Oxidative cleavage of **8** (3.2 equiv of $NaIO_4$ and 0.5 equiv of OsO_4 in 1:1 *t*-BuOH–H_2O at 23 °C for 1 h) formed seco acid **9** (100% yield), which upon treatment with 4.5 equiv of $MeSO_3H$ and 4 Å molecular sieves in CH_2Cl_2 at −20 °C for 1 h yielded the tricyclic lactone **10** (68% as a 9:1 mixture of anomers at the methoxylated carbon). Exposure



of **10** (9:1 mixture) to 1.4 equiv of thiophenol and 1.4 equiv of BF_3·Et_2O in CH_2Cl_2 at 0 °C for 1.75 h gave exclusively the

(1) (a) Corey, E. J.; Sarshar, S.; Lee, D.-H. *J. Am. Chem. Soc.* **1994**, *116*, 12089. (b) Corey, E. J.; Lee, D.-H., Sarshar, S. *Tetrahedron Asymmetry* **1995**, *6*, 3.

(2) See also: (a) Corey, E. J.; Sarshar, S.; Bordner, J. *J. Am. Chem. Soc.* **1992**, *114*, 7938. (b) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (c) Corey, E. J.; Imai, N.; Pikul S. *Tetrahedron Lett.* **1991**, *32*, 7517.

(3) For recent review of catalytic enantioselective Diels–Alder reactions, see: (a) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (b) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497. (c) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741. (d) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763.

(4) (a) Mayol, L.; Piccialli, V.; Sica, D. *J. Nat. Prod.* **1986**, *49*, 823; (b) *Tetrahedron* **1986**, *42*, 5369; (c) *Tetrahedron Lett.* **1985**, *26*, 1253.

(5) Hosomi, A.; Saito, M.; Sakurai, H. *Tetrahedron Lett.* **1979**, *20*, 429. The acid sensitivity of the *N*-arylmaleiimide adducts with 2-methoxybutadiene created major problems in subsequent steps, and therefore, this route was less suitable for the synthesis of **1** and **2**.

(6) The enantiomeric ratio 97.5:2.5 of adduct **4** was determined by HPLC analysis using a Chiralcel OJ column (Chiral Technologies Inc.) with 0.1% isopropyl alcohol in hexane as eluant (relative retention times 19.4 (minor) and 29.0 (major) min).

(7) The formation of adduct **4** in the Diels–Alder reaction catalyzed by the chiral diazaaluminolidine **3** follows from the qualitative electronic equivalence of MeO and Me_3SiCH_2 groups as electron-donating groups and the transition-state model proposed earlier (ref 1).

(8) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800.

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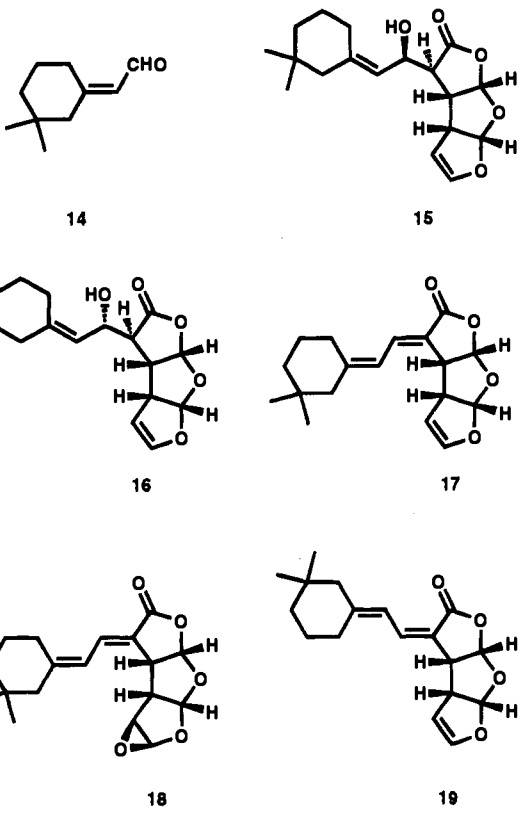
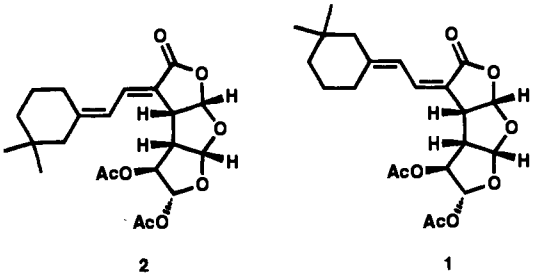
phenylthio ether **11** (52%), which was oxidized to the corresponding sulfoxide **12** with 1 equiv of *m*-chloroperbenzoic acid in CH_2Cl_2 at −20 °C for 1.5 h. The tricyclic vinyl ether−lactone **13** was generated in 100% yield (overall from **11**) by heating sulfoxide **12** in $CHCl_3$ at 65 °C for 14 h.

Deprotonation of the tricyclic lactone **13** (1.3 equiv of *t*-BuLi in THF at −78 °C for 25 min), treatment of the resulting lithium enolate with 3.5 equiv of anhydrous $ZnCl_2$ (−78 °C for 10 min), and further reaction with the (*E*)-aldehyde **14**[9] (1.9 equiv at −78 °C for 20 h) produced in 100% yield a 79:21 mixture of β-diastereomeric aldols **15** and **16**, which were readily separated by silica gel column chromatography and which could each be converted to triene lactone **17** in the following way.[10] Aldol adduct **15** was transformed into triene **17** by (1) acetylation using excess Ac_2O−Et_3N and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine at 23 °C for 40 min (91% yield) and elimination of acetic acid using 2.7 equiv of diazobicycloundecane in DMF−DME at 80 °C for 3 h (91% yield); for **17**, $[\alpha]^{23}_D$ +309° (*c* = 1.2 in $CHCl_3$). Aldol adduct **16** afforded **17** upon



dehydration with 4 equiv of dicyclohexylcarbodiimide and a catalytic amount of cupric chloride in ether at 23 °C for 18 h (90% yield).[11] Triene lactone **17** was converted to gracilin C (**2**) in 78% overall yield by the following three-step sequence: (1) selective epoxidation at the *exo* face at the dihydrofuran subunit to form **18** (2.7 equiv of dimethyldioxirane in CH_2Cl_2 at −20 °C for 20 min), (2) acetolysis of **18** (excess HOAc in CH_2Cl_2 at −30 °C for 1 h and then at −15 °C for 3.5 h) to give the corresponding 2-*endo*-hydroxy-3-*exo*-acetoxytetrahydrofuran, and (3) acetylation (excess Ac_2O−Et_3N and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine in CH_2Cl_2 at 23 °C for 20 min). Aldol adduct **15** was transformed into gracilin B (**1**) by stereospecific dehydration using dicyclohexylcarbodiimide−$CuCl_2$ in ether at 23 °C for 36 h to form triene lactone **19**, $[\alpha]^{23}_D$ +261° (*c* = 5.8 in $CHCl_3$), and then application to **19** of the three-step sequence outlined above for the synthesis of gracilin C from triene lactone **17** (epoxidation, acetolysis, and acetylation; overall yield, 73%). The rotation observed for synthetic gracilin C was $[\alpha]^{23}_D$ +277° (*c* = 1.3 in $CHCl_3$), and that for synthetic gracilin B was $[\alpha]^{23}_D$ +119° (*c* = 1.2 in $CHCl_3$).[12] The NMR, infrared, ultraviolet, and mass spectral data were in complete agreement with those previously reported.[4]



The enantioselective total synthesis of gracilins B and C from a common intermediate which is described herein demonstrates clearly the power of the diazaaluminolidine-catalyzed Diels−Alder reaction using a readily available and recoverable chiral ligand.[1,2] Although the whole synthesis rests on the initial Diels−Alder step,[13] there are a number of other noteworthy transformations including (1) the method used for the conversion of the succinimide unit to the 2,5-dimethoxytetrahydrofuran unit in **7**, (2) the cleavage of the carbocyclic system of **7** to generate keto acid **9**, (3) the stereocontrol of the aldol coupling to form either **17** or **19**, and (4) the selective epoxidation to form **18**. The synthetic sequence was also executed starting with (±)-**4** to produce racemic gracilins B and C.

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Supporting Information Available: Experimental procedures for each step in the synthesis of **1** and **2** complete with spectral data (18 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(9) Prepared according to the following: (a) Pelletier, S. W.; Mody, N. V. *J. Org. Chem.* **1976**, *41*, 1069. (b) de Souza, J. P.; Goncalves, A. M. R. *J. Org. Chem.* **1978**, *43*, 2068.

(10) The aldol reaction of **13** and **14** was completely face selective with regard to the enolate component.

(11) (a) Corey, E. J.; Anderson, N. H.; Carlson, R. M.; Paust, J.; Vedejs, E.; Vlattas, I.; Winter, R. E. *J. Am. Chem. Soc.* **1968**, *90*, 3245. (b) Alexandre, C.; Rouessac, F. *Tetrahedron Lett.* **1970**, 1011.

(12) The observed rotation for **2** agrees exactly with that reported. There is a discrepancy between that which we measured for synthetic **1** (+119°) and that reported[4] (+191°) which we believe is due to a typographical error in the report of the latter.

(13) For the application of other catalytic enantioselective Diels−Alder reactions to the synthesis of structurally complex natural products, see: Corey, E. J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611.