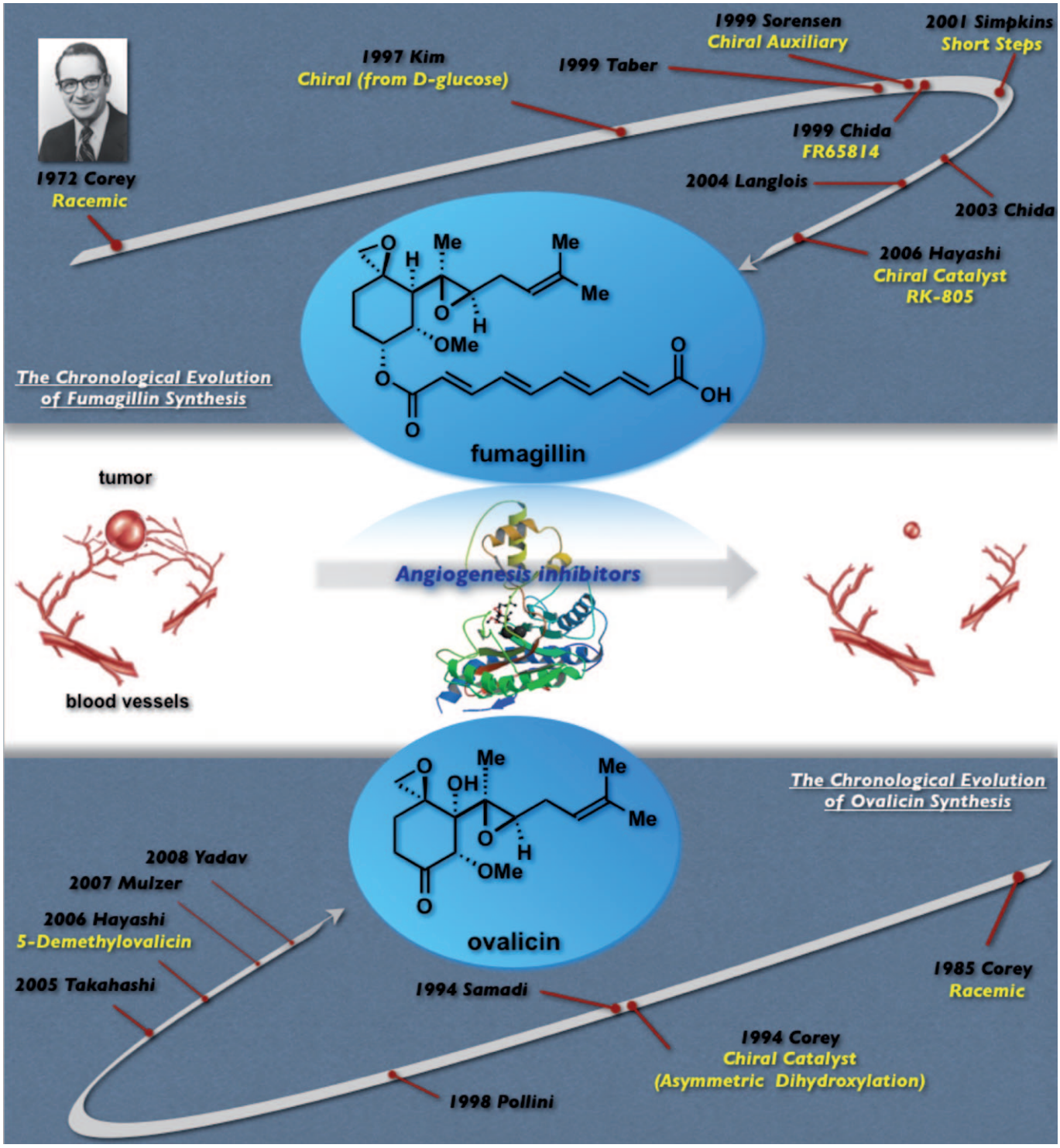
CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200902433

Syntheses of Fumagillin and Ovalicin

Junichiro Yamaguchi[a] and Yujiro Hayashi*[b]



Abstract: This review focuses on the synthetic strategies used for the construction of fumagillin, ovalicin, and other natural products of this family that are known angiogenesis inhibitors. These compounds are comprised of a cyclohexane framework, two epoxides, and five or six contiguous stereogenic centers. The first total syntheses of fumagillin and ovalicin were reported by Corey in 1972 and 1985, respectively. There were numerous studies directed at these natural products in the decades that followed with many reports appearing in the year 2000 or later. Despite the relatively small size of these molecules, their syntheses highlight the efficient construction of stereogenic centers in organic synthesis.

Keywords: angiogenesis · fumagillin · ovalicin · natural products · total synthesis

Introduction

Angiogenesis, the formation of new blood vessels from preexisting vasculature, has been implicated in the pathogenesis of several human diseases, including tumor growth, rheumatic arthritis, atherosclerosis, and macular degeneration.[1] Folkman first suggested the concept of treating solid cancers by inhibiting angiogenesis in 1971,[2] and in recent years, numerous researchers have been searching for inhibitors of angiogenesis as an opportunity to inhibit the above diseases.

Fumagillin (**1**; Figure 1), isolated in 1949 by Elbe and Hanson[3] from the microbial organism *Aspergillus fumigatus*, was originally described as an antimicrobial agent, but in 1990, it was reported to be a potent, selective inhibitor of angiogenesis.[4] Semisynthetic compounds, such as TNP-470[4a] (**2**; also known as AGM1970) and CKD-732 (**3**),[5] underwent trials for the treatment of a variety of cancers. Ovalicin (**8**)[6] also inhibits angiogenesis and is more stable than **1** or **2**, whereas the recently isolated 5-demethylovalicin (**9**)[7] was found to be as potent an angiogenesis inhibitor as **8**. Chlovalicin[8] was isolated together with **8** from *Sporothrix* sp. FO-4649 1 by Omura. Compounds **1**, **2**, and **8** have been shown to specifically bind to type 2 methionine aminopeptidase (MetAP2).[9]

Recently, Osada, Kakeya, and co-workers isolated RK-805 (**7**) from the fungus *Neosartora* sp.[10] and RK-95113 (**4**) from *Aspergillus fumigatus* var. *fumigatus* sp.,[11] both of which are inhibitors of angiogenesis. Although all these natural products are anti-angiogenesis compounds, FR65814 (**6**),[12] despite its similar structure, displays a completely different biological activity, that of an immunosuppressant. More recently, fumagillin (**1**) has been found to reverse the growth inhibitory activity of Viral protein R (Vpr) in yeast and human cells, and to inhibit the HIV-1 infection of human macrophages.[13]

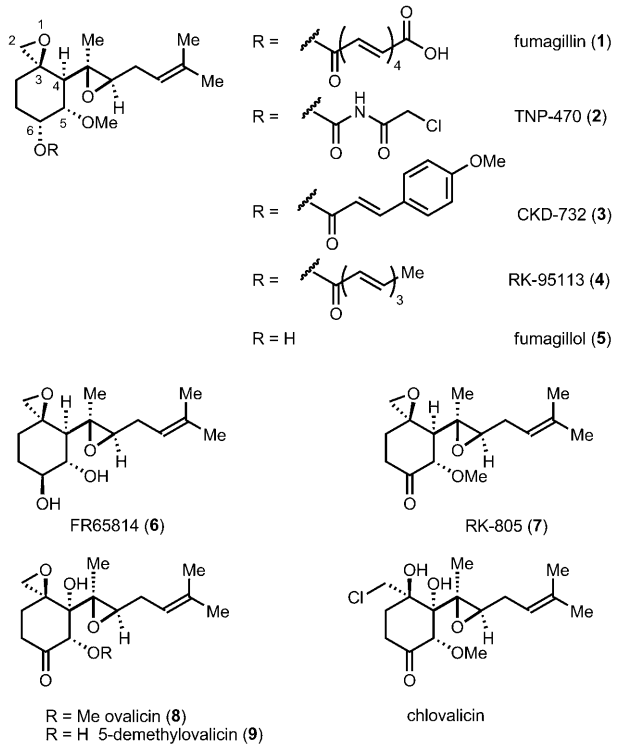


Figure 1. Fumagillin and ovalicin analogues.

Structurally, these compounds are all comprised of a cyclohexane framework, two epoxides, and five or six contiguous stereogenic centers, three or four of which are situated on the cyclohexane ring. As a result of their unique structures and important biological properties, the fumagillins and ovalicins, as well as their congeners, have been pursued as attractive synthetic targets. This review aims to provide a detailed overview of the reported synthetic strategies to access fumagillin and ovalicin derivatives.

[a] Dr. J. Yamaguchi
Department of Chemistry
Graduate School of Science, Nagoya University
Furo-cho, Chikusa, Nagoya 464-8602 (Japan)

[b] Prof. Dr. Y. Hayashi
Department of Industrial Chemistry, Faculty of Engineering
Tokyo University of Science
Kagurazaka, Shinjuku-ku, Tokyo 162-8601 (Japan)
Fax: (+81) 3-5261-4631
E-mail: hayashi@ci.kagu.tus.ac.jp

Overview of Synthetic Strategies

Fumagillin (**1**) and its simpler congener fumagillol (**5**) have attracted significant synthetic interest, beginning as early as the 1960s. In 1972, the first total synthesis of racemic **1** was reported by the group of Corey,[14] and following this pioneering work, this molecule lay dormant for 25 years. In 1997, Kim and co-workers[15] completed the first asymmetric synthesis of (−)-**5**. Over the past 11 years, two racemic syntheses (Sorensen[16a] and Simpkins[17]) and five asymmetric syntheses, which includes two formal syntheses (Taber,[18] Eustache,[19] Chida,[20c] Sorensen,[16b] Langlois,[21c] and Hayashi[22]), were reported. Figure 2 depicts a graphical summary of the syntheses of **1** and **5**, along with their key retrosynthetic disconnections. A common feature to all the synthetic routes is the introduction of the side-chain epoxide at a late stage in the synthesis. The C5 and C6 stereocenters (see carbon numbering in Figure 1) have been constructed by stereoselective reactions or have originated from a chiral starting material. The groups of Corey, Sorensen, Chida, and Langlois all introduce this pair of stereocenters by dihydroxylation of the corresponding cyclohexene derivative. The groups of Taber and Hayashi constructed this diol motif through Rubottom oxidation, followed by diastereoselective reduction of the resulting ketone. In contrast, Kim and co-workers conserved the two stereocenters present in D-glucose throughout their entire synthesis. The key C4 stereogenic center was introduced by a variety of methods: The group of Corey used a Diels–Alder reaction, whereas the groups of Kim, Chida, and Langlois employed an Ireland–Claisen rearrangement; the groups of Sorensen, Taber, Simpkins, and Hayashi introduced this stereocenter by conjugate addition to a cyclohexanecarbaldehyde or a cyclohexenone derivative, or by a nucleophilic opening of an epoxycyclohexane; Eustache and co-workers used the venerable Evans aldol chemistry[23] on an acyclic system to generate the C4 and C5 stereocenters concomitantly. To assemble the C3 stereocenter, the groups of Taber, Chida, Eustache, and Simpkins, epoxidized a ketone functionality by using either the Corey–Chaykovsky reagent[24] or chloromethyllithium; Corey generated this stereocenter through the inversion of a bromoalcohol, whereas Kim and co-workers made use of an intramolecular nucleophilic displacement reaction. Among the most recent syntheses of **5**, Sorensen and co-workers used an elegant [3,3] sigmatropic rearrangement to induce asymmetry at C3, whereas our group introduced the same stereocenter by a diastereoselective cyanosilylation reaction.

Studies toward the synthesis of **8** were initiated by Corey's group in 1985.[25a] Nine years thereafter, Samadi and co-workers[26] accomplished the first asymmetric synthesis of **8**, which was followed by Corey's own asymmetric version of the total synthesis later that year.[25b] In the following years, five syntheses of **7** were reported by the groups of Pollini,[27] Takahashi,[28] Hayashi,[22] Mulzer,[29] and Yadav.[30] The key traits of each synthesis are summarized in Figure 3. A common feature to all approaches is the late stage introduction of the side-chain epoxide, similar to the syntheses of **1**. In addition, all strategies introduced the aliphatic side chain through a coupling of the epoxyketone derivatives. The groups of Samadi, Pollini, Takahashi, and Yadav prepared the C5 stereocenter from a natural chiral template, whereas the group of Corey generated the stereocenter by inversion of a bromide. In contrast, Mulzer utilized a dihydroxylation method, and we examined a [VO(O*i*Pr)$_3$]-mediated epoxidation route.

Various strategies were employed to introduce the required asymmetry in these optically active compounds: 1) Utilization of the chiral pool, namely, starting from quinic acid and quebrachitol for **8**, glycidol for **1**, glucose and mannitol for **5**, and glucose for **6**; 2) clever manipulation of chiral auxiliaries in the diastereoselective syntheses of **5**, reported by the groups of Sorensen and Eustache; 3) successful inclusion of catalytic asymmetric induction methods, namely, Corey's synthesis of **8** through substrate-enhanced asymmetric dihydroxylation, as well as, our syntheses of compounds **5**–**9** by way of α-aminoxy oxidation.[31] Details of the reported syntheses of fumagillin, ovalicin, and their derivatives are described, herein, in chronological order.

Junichiro Yamaguchi was born in 1979 in Tokyo (Japan). He received his Ph.D. in 2007 from the Tokyo University of Science under the supervision of Professor Yujiro Hayashi. From 2007 to 2008, he was a postdoctoral fellow in the group of Professor Phil S. Baran at the Scripps Research Institute (JSPS postdoctoral fellowships for research abroad). In 2008, he became an assistant professor at Nagoya University working with Professor Kenichiro Itami. His research interests include the total synthesis of natural products and the innovation of synthetic methods.

Yujiro Hayashi was born in 1962 in Gunma (Japan), and received his B.Sc. in 1984 and M.Sc. in 1986 from the University of Tokyo under the guidance of Professor Teruaki Mukaiyama. He received a Ph.D. degree from the same university under the supervision of Professor Koichi Narasaka, after which he was appointed as assistant professor at the University of Tokyo in 1987, working with Professor Koichi Narasaka. From 1994 to 1996, he undertook postdoctoral study at Harvard University under the supervision of Professor E. J. Corey. He moved to Tokyo University of Science, thereafter, as an associate professor in 1998 and was promoted to full Professor in 2006. He was honored with an incentive award in synthetic organic chemistry (Japan) in 1998 and an SSOCJ Daiichi–Sankyo award for medicinal organic chemistry in 2008. His current interests are the development of new synthetic reactions in the field of organocatalysis and the total synthesis of biologically active natural products.

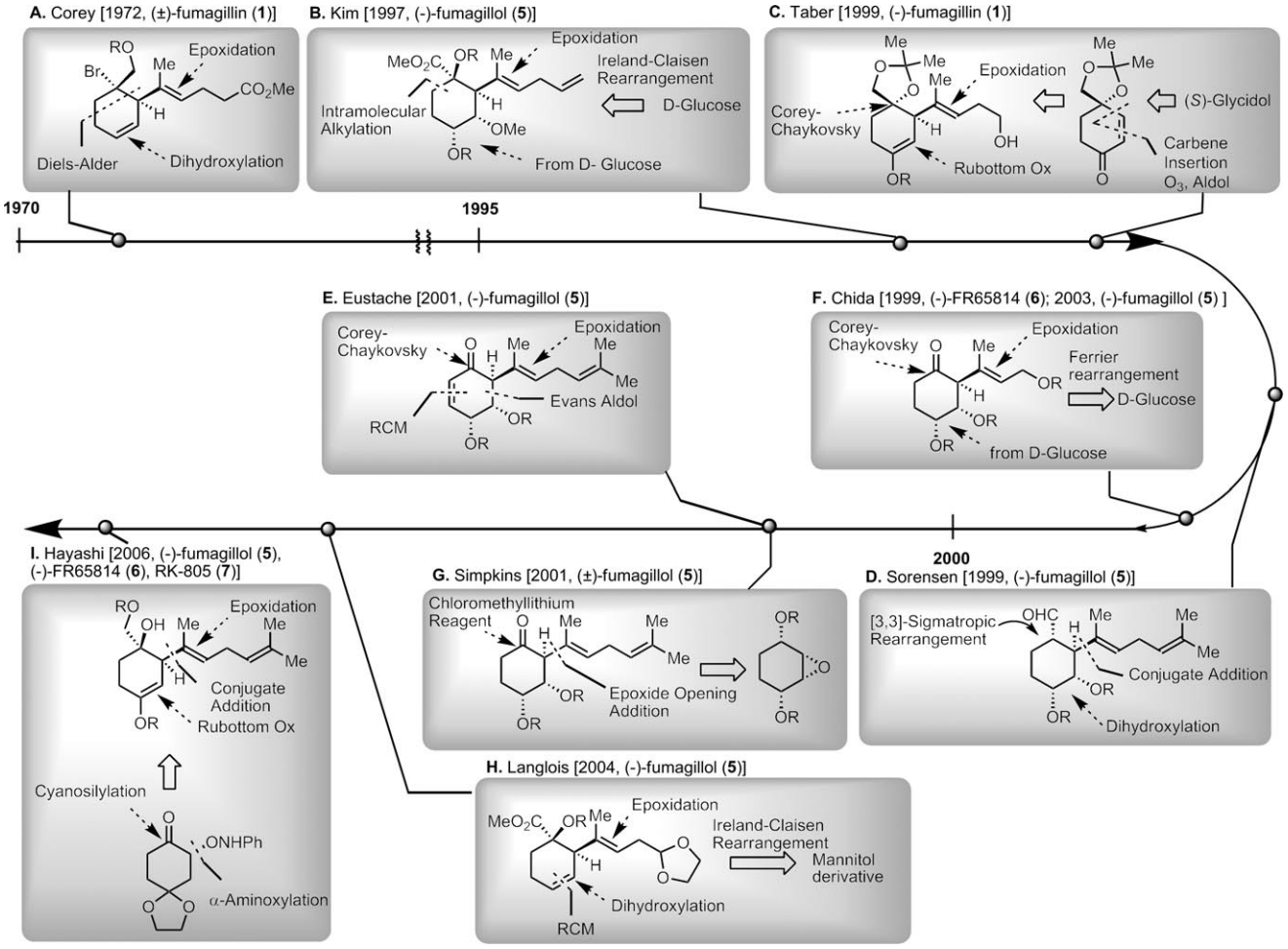


Figure 2. A timeline portraying the chronological evolution in the synthetic strategies employed to access **1** and **5**.

Total Syntheses of Fumagillin, Fumagillol, FR65814, and RK-805

Corey's synthesis:[14] In 1972, the group of Corey reported the first total synthesis of racemic **1** by using a Diels–Alder cycloaddition as their key step (Scheme 1). The known compound, 5-methyl-4-hexenoate (**11**), obtained in two steps[32] from 3,3-dimethylallyl bromide (**10**), was oxidized with selenium dioxide giving the α,β-unsaturated aldehyde **12** in a stereoselective manner. Wittig reaction of aldehyde **12** with allylidenetriphenylphosphorane (**13**) gave a mixture of 4*E* and 4*Z* isomers, which was subsequently equilibrated to cleanly produce the (4*E*,6*E*)-triene **14**. The reaction of **14** with α-bromoacrolein at reflux in benzene gave a high yield (80%) of the Diels–Alder adduct **15**, which proved to be the desired isomer. After the two-step transformation of the aldehyde to the TMS ether **17**, a stereoselective epoxidation of the trisubstituted olefin was followed by spiroepoxide formation with inversion of configuration to generate the bis-epoxide **18**. Dihydroxylation of cyclohexene **18** proceeded with a high degree of stereocontrol, to afford diol **19** in 81% yield from **18** (diastereomeric ratio (d.r.) = 9:1). Careful exposure of diol **19** to 1.3 equivalents of sodium *tert*-amylate and excess iodomethane resulted in selective methylation of the C5 alcohol in 65% yield based on recovered starting material (47% yield of the isolated product). The side-chain ester was converted into the corresponding tertiary alcohol and then selective acetylation of the secondary alcohol gave **20**. Dehydration of tertiary alcohol **20** was accomplished by mesylation, followed by TBAB-induced elimination, to afford the desired dehydrated product as the major isomer (in a 3:1 ratio). After removal of the acetyl protecting group, the first total synthesis of **5** was complete. The side chain of **1** was then introduced by treatment of **5** with methyllithium, followed by addition of decatetraenedioyl chloride (**21**) (derived from the degradation of natural **1**) to give racemic **1**. Overall, this elegant sequence required 16 steps to obtain **1** and proceeded with an astounding level of efficiency and stereocontrol, despite its completion being 27 years ago.

Kim's synthesis:[15] In 1997, Kim and co-workers reported the first asymmetric synthesis of (−)-**5** by using an Ireland–Claisen rearrangement and enolate alkylation as key steps (Scheme 2). The synthesis commenced with the readily available diol **22** (derived from D-glucose)[33], and it was con-

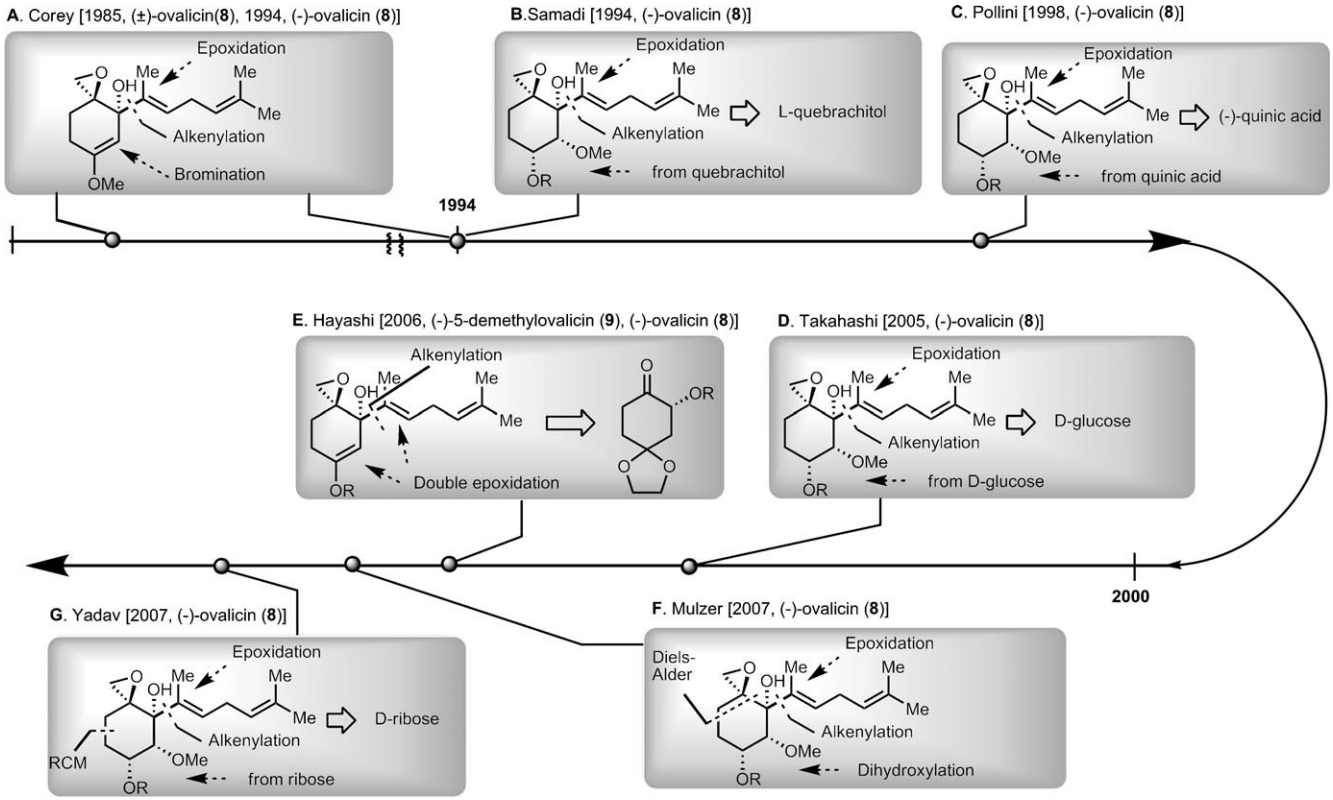
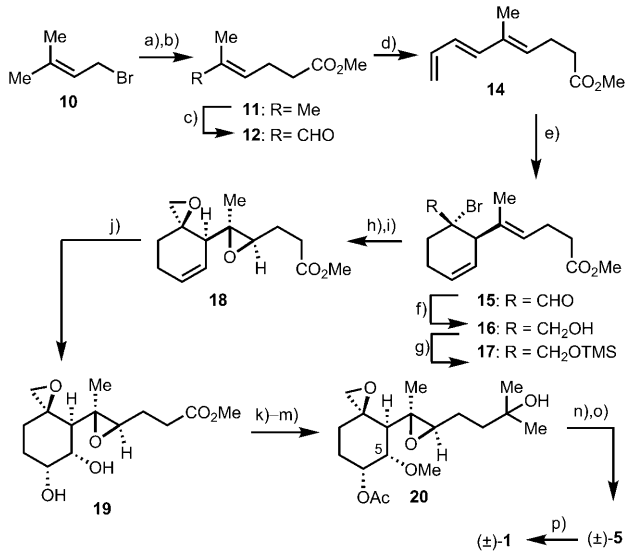


Figure 3. A timeline portraying the chronological evolution in the synthetic strategies employed to access **8**.

verted into alcohol **23** in seven straightforward steps. Conversion of the dihydroxyester **23** into aldehyde **24** was achieved by TBDPS protection of the primary alcohol, benzyl protection of the secondary alcohol, reduction of the ester into a primary allylic alcohol, followed by MnO_2 oxidation of the resulting alcohol. Allylation of **24** with allylmagnesium bromide afforded a 1:1 mixture of α- and β-hydroxy products, **25a** and **25b**. Both isomers were easily converted into the desired ester **26** in one step: DCC coupling of β-alcohol **25b** or Mitsunobu inversion[34] of α-alcohol **25a**. Ireland–Claisen rearrangement,[35] induced by sequential treatment of **26** with LHMDS followed by TMSCl and NEt_3, via intermediate **27**, gave the desired C4 stereocenter with a high degree of selectivity. After exchange of the TBDPS group of **28** for a *p*-toluenesulfonyl (tosyl/Ts) group, the C1 stereogenic center was diastereoselectively generated from **29** by intramolecular alkylation of the intermediate enolate **30**, affording the cyclic product **31** (d.r. 11:1). Compound **31** was then converted to epoxide **32** through four synthetic operations, namely, reduction of the methyl ester, benzyl group removal, selective tosylation of the resulting primary alcohol, and formation of the epoxide by using K_2CO_3 in MeOH. The *meta*-chloroperbenzoic acid (*m*CPBA) epoxidation procedure in the presence of $NaHCO_3$ resulted in a highly chemo- and stereoselective epoxidation (d.r. 11:1) of the trisubstituted olefin, providing **33** in 92% yield. Finally, a conventional two-step ozonolysis/Wittig olefination sequence was required to complete (−)-**5** in 45% yield from **33**. The completion of this first asymmetric total synthesis of (−)-**5** over the course of 25 synthetic operations stands as an impressive accomplishment to this day.

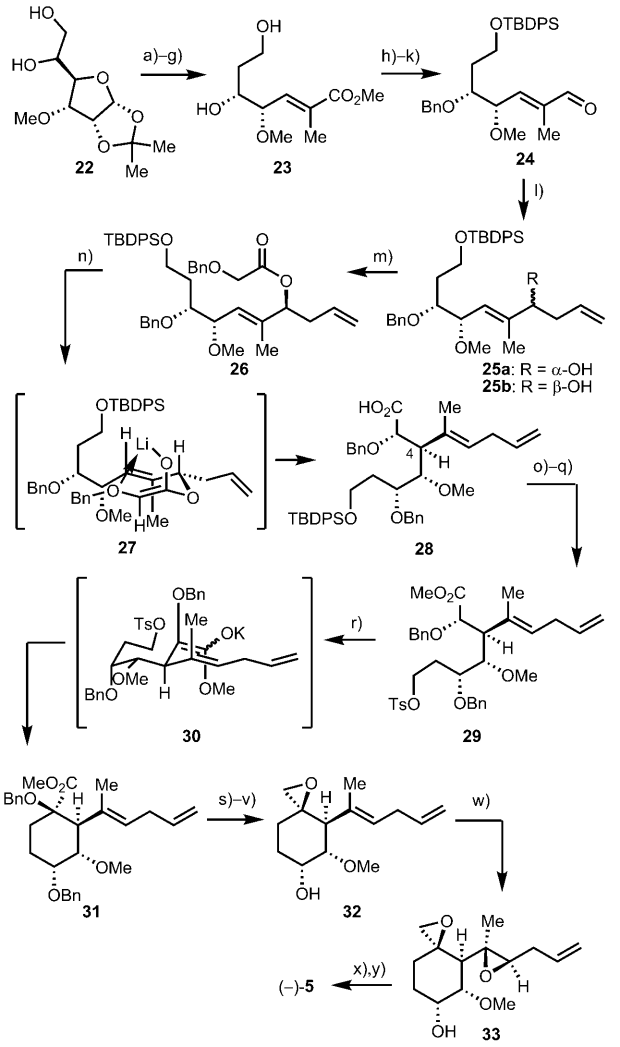
Taber's synthesis:[18] The second enantioselective synthesis of **1** was accomplished by Taber et al., by utilizing a stereoselective carbene insertion[36] and conjugate addition of a vinyl cuprate reagent as key steps (Scheme 3). Starting from commercially available (*S*)-glycidol (**34**), a standard two-step transformation afforded acetonide **35** in 90% yield from **34**. The key intermediate, alkylidene carbene **36** (generated in situ by using Br_2 and KHMDS), produced C−H insertion product **37**, which was then carried forward to **38** through ozonolysis followed by aldol condensation. Conjugate addition onto **38** by using an organocuprate reagent generated from **39**, followed by enolate trapping with TESCl produced silyl enol ether **40** with excellent diastereocontrol (d.r. 96:4). Rubottom oxidation[37] proceeded by treatment of silyl enol ether **40** with *m*CPBA, which was followed by selective removal of the TES group by using TBAF, to yield α-hydroxyketone **41**. Methylation of the hydroxyl unit in **41**, diastereoselective ketone reduction with L-selectride, benzoylation of the resulting alcohol and concomitant deprotection of the acetal and TBS groups gave compound **42**. Overall inversion of the C3 center was achieved in two steps, consisting of oxidative diol cleavage and subsequent Corey–Chaykovsky reaction,[24] to afford epoxide **43** as a single diastereomer (78% yield over two steps).



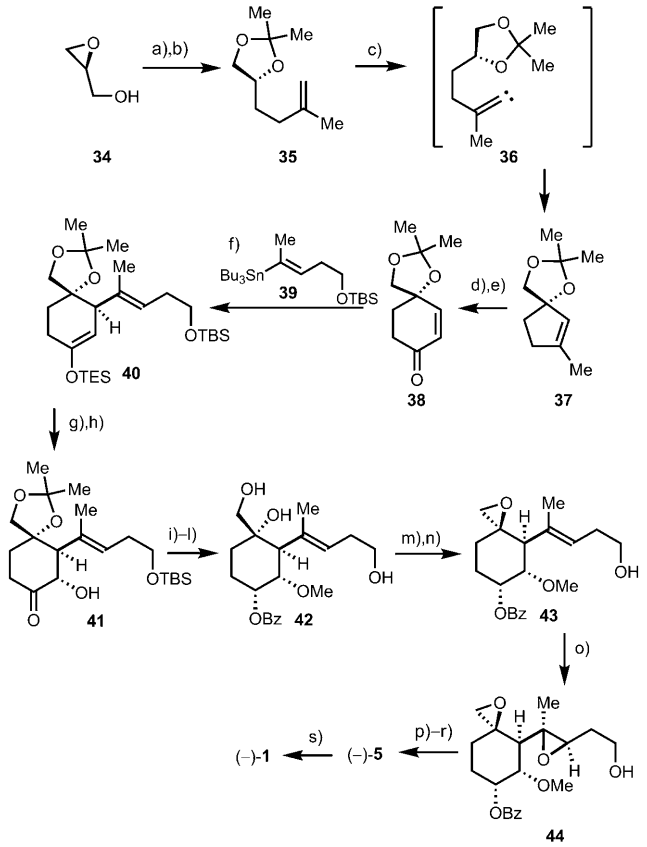
Scheme 1. Corey's first total synthesis of (±)-**5** and (±)-**1**. Reagents and conditions: a), b) see ref. [32], 57%; c) SeO_2, DME (aq), reflux, 41%; d) allylidenetriphenylphosphorane (**13**), THF, −20 to 25°C, 84% (*E*/*Z* = 1:1) then 80°C, >95% single isomer; e) α-bromoacrolein, K_2CO_3, hydroquinone, benzene, reflux, 80%; f) $NaBH_4$, THF (wet), >98%; g) TMSCl, NEt_3, THF, 25°C, 90%; h) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0°C, 80% (d.r. 9:1 in favor of desired diastereomer); i) TBAF, THF; then NaOMe; j) OsO_4, pyridine, 81% over two steps (d.r. 9:1 in favor of desired diastereomer); k) MeI (excess), sodium *tert*-amylate, THF, 47% (65% BRSM); l) MeLi, THF, −78°C, 75%; m) Ac_2O, pyridine, 50°C, 95%; n) MsCl, NEt_3, −15°C, THF; then TBAB, THF, 25°C (d.r. 3:1 in favor of desired isomer); o) K_2CO_3, MeOH; p) MeLi, decatetraenedioyl chloride, −78°C. DME = 1,2-dimethoxyethane, TMSCl = trimethylsilylchloride, *m*CPBA = *m*-chloroperbenzoic acid, TBAF = tetrabutylammonium fluoride, TBAB = tetrabutylammonium bromide, BRSM = based on recovered starting material, Ms = methanesulfonyl.

Epoxidation of **43** gave **44**, again as a single isomer. The trisubstituted olefin in the side chain was constructed by primary alcohol oxidation followed by Wittig olefination, and a final debenzoylation step gave (−)-**5** in good yield (77% over three steps). Finally, (−)-**5** was converted into (−)-**1** by the method previously described by Corey (Scheme 1), thus, the total synthesis of **1** was accomplished in 19 steps. In summary, Taber achieved a concise, stereoselective synthesis of **1** in which the C4 and C5 stereocenters were constructed by the addition of a side-chain organocuprate to an enone followed by Rubottom oxidation, an approach highly distinctive from the Corey and Kim syntheses.

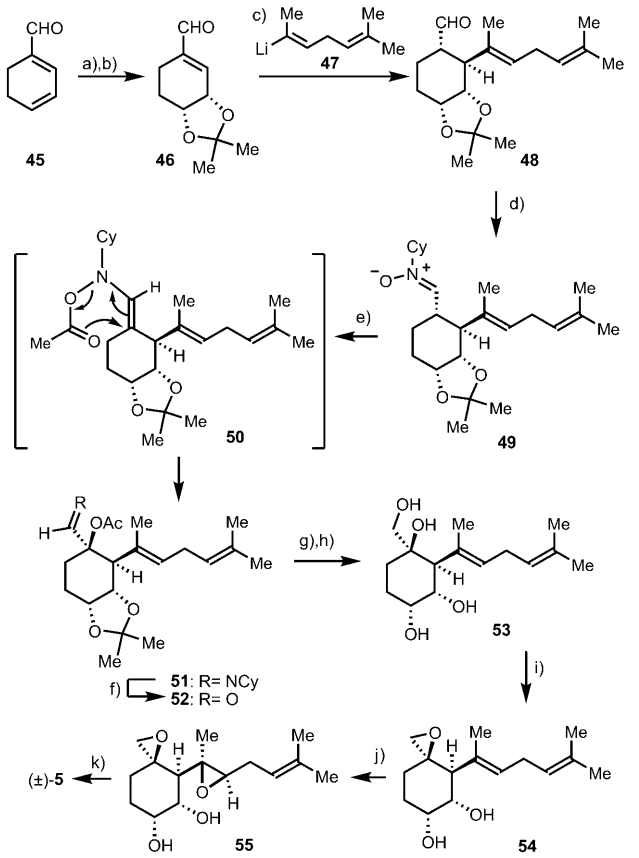
Sorensen's synthesis:[16] Concurrently with Taber's report, the Sorensen group reported an alternative synthesis of racemic **5** that devised a conjugate addition of the alkylidene lithium reagent **47** onto enal **46** (Scheme 4). Known 1,3-cyclohexadiene-1-carbaldehyde (**45**)[38] was carefully chosen as the starting material and was transformed into **46** in 64% yield over two steps. Enal **46** was treated, under $BF_3{\cdot}OEt_2$ catalysis, with an organocuprate reagent generated from **47**[25a,41] to afford the 1,4-addition product **48**. Although aldehyde **48** was obtained in 47% yield in only a suboptimal 3:1 ratio of C3 epimers (favoring the desired product), the



Scheme 2. Kim's first asymmetric total synthesis of (−)-**5**. Reagents and conditions: a) MsCl, NEt_3, CH_2Cl_2, −30 to −20°C; b) NaI, methyl ethyl ketone, 100°C, 77% over two steps; c) 9-BBN, THF, −40 to 23°C; then 30% H_2O_2, 3N NaOH, 60 to 70°C, 93%; d) Dowex 50, H_2O, 100°C; e) $NaIO_4$, acetone/H_2O (2:1); f) $Ph_3P{=}C(CH_3)CO_2Me$, CH_3CN, 100 to 110°C; g) K_2CO_3, MeOH, 23°C, 63% over four steps; h) TBDPSCl, DMAP, NEt_3, CH_2Cl_2, 23°C, 93%; i) $CCl_3(C{=}NH)OBn$, cat. CF_3SO_3H, cyclohexane/CH_2Cl_2 (2:1), 23°C; j) DIBAL-H, toluene, −78°C, 89% for two steps; k) MnO_2, CCl_4, 23°C, 90%; l) $CH_2{=}CHCH_2MgBr$, THF, −78 to 0°C, 84%; m) i) β-OH; $BnOCH_2CO_2H$, DMAP, DCC, CH_2Cl_2, 23°C, 100%; ii) α-OH; DIAD, $BnOCH_2CO_2H$, Ph_3P, THF, 0 to 23°C, 83%; n) LHMDS, TMSCl/NEt_3 (1:1.1), THF, −78 to 23°C (a single diastereomer); o) Triton B, MeI, THF, 23°C, 89%; p) TBAF, THF, 23°C, 95%; q) TsCl, pyridine, $CHCl_3$, −20°C; r) KHMDS, THF, −45 to −40°C, 64% over two steps (d.r. 11:1 in favor of desired diastereomer); s) DIBAL-H, toluene, −78°C, 87%; t) excess Li, NH_3, −78°C, 90%; u) TsCl, NEt_3, DMAP, CH_2Cl_2, 23°C; v) K_2CO_3, MeOH, 23°C, 88% for two steps; w) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0°C, 92%; x) O_3, ethyl acetate, −78°C; y) excess $Ph_3P{=}C(CH_3)_2$, THF, −78 to 23°C, 45% for two steps. 9-BBN = 9-borabicyclo[3.3.1]nonane, DMAP = *N*,*N*-dimethyl-4-aminopyridine, TBDPS = *tert*-butyldiphenylsilyl, Bn = benzyl, DIBAL-H = diisobutylaluminium hydride, DCC = dicyclohexylcarbodiimide, LHMDS = lithium hexamethyldisilazide, DIAD = azodicarboxylic acid diisopropyl ester, Ts = tosyl, Triton B = benzyltrimethylammonium hydroxide, KHMDS = potassium hexamethyldisilazide.



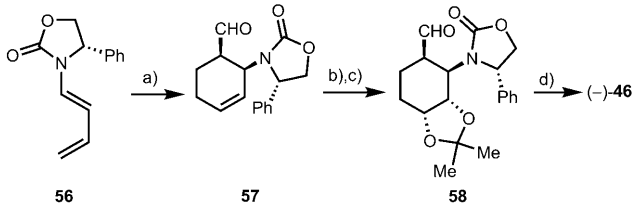
Scheme 3. Taber's synthesis of (−)-**1**. Reagents and conditions: a) Methallyl chloride, Mg, Et_2O, 0 °C, then −78 to 23 °C; b) TsOH, 2,2-dimethoxypropane, 23 °C, 90% over two steps; c) Br_2, Et_2O, −78 °C; then KHMDS, −65 to 23 °C, 72%; d) O_3, CH_2Cl_2, −78 °C; then Ph_3P, 23 °C, 82%; e) KOH, CH_2Cl_2, 23 °C, 85%; f) compound **39**, *n*BuLi, CuCN, THF, −60 to −10 °C; then TESCl, NEt_3, THF −60 to 23 °C, 74%; g) *m*CPBA, hexane, −30 to −10 °C; h) TBAF, NH_4Cl, THF, −30 to −10 °C, 55% over two steps; i) MeI, Ag_2O, CH_3CN, 23 °C; j) L-selectride, THF, −78 °C, 66% over two steps; k) BzCl, pyridine, CH_2Cl_2, 0 °C; l) Dowex 50, MeOH, 23 °C, 52% over two steps; m) $NaIO_4$, CH_2Cl_2, H_2O, $NaHCO_3$, 0 to 23 °C; n) $Me_3S^+OI^-$, NaH, THF, DMSO, 0 to 23 °C, 78% over two steps; o) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 77%; p) Dess–Martin periodinane (DMP), CH_2Cl_2, 0 to 23 °C; q) $Ph_3P{=}C(CH_3)_2$, THF, −78 °C, 86% over two steps; r) K_2CO_3, MeOH, 0 to 23 °C, 89%; s) MeLi, decatetraenedioyl chloride (**21**), THF, −78 °C, 75%. TESCl = triethylsilyl chloride, L-selectride = lithium tri-*sec*-butyl(hydrido)borate, Bz = benzoyl, TBS = *tert*-butyldimethylsilyl.



Scheme 4. Sorensen's synthesis of (±)-**5**. Reagents and conditions: a) OsO_4, NMO·H_2O, 2-propanol, 23 °C, 73%; b) acetone, TsOH, 23 °C, 87%; c) compound **47**, Li(2-thienyl)CuCN; then **46**, BF_3·OEt_2, Et_2O, 46% (a 3:1 mixture of C3 epimers in favor of **48**; d) $C_6H_{11}NHOH$, EtOH, $NaHCO_3$, 23 °C; e) AcCl, Et_3N, Et_2O, 23 °C; f) AcOH, NaOAc, 23 °C, 51% over three steps; g) $LiAlH_4$, Et_2O, 23 °C, 71%; h) 2 N HCl/THF (4:1), 23 °C, 81%; i) MsCl, DMAP, NEt_3, CH_2Cl_2; then 6 N NaOH, MeOH, 23 °C, 97%; j) cat. [VO(acac)$_2$], *t*BuOOH, benzene, 23 °C, 75% (4.3/1 ratio of epoxide diastereomers in favor of **55**); k) NaO*t*Bu, MeI, THF, 15-crown-5, 23 °C, 40% of **5** plus 40% recovered **55**. Cy = cyclohexyl, NMO = *N*-methylmorpholine *N*-oxide, TsOH = *p*-toluenesulfonic acid, [VO(acac)$_2$] = vanadyl acetylacetonate.

minor epimer could be converted into **48** upon epimerization with *t*BuOK in *t*BuOH. To construct the C3 quaternary center, aldehyde **48** was treated with *N*-cyclohexylhydroxylamine, and acetylation of the resulting *N*-cyclohexylnitrone **49** induced a [3,3] sigmatropic rearrangement[39] to give imine **51**. Hydrolysis of **51** under mild conditions then afforded aldehyde **52** (in 51% yield from **49**). Simultaneous reduction of both carbonyl moieties with lithium aluminum hydride was then followed by acetal hydrolysis, to produce tetraol **53** in a two-step yield of 58%. Selective monomesylation of tetraol **53** was achieved at low temperatures, and alkaline treatment of the resulting primary mesylate led to the desired epoxide **54**. Introduction of the second oxirane functionality was achieved by vanadium-catalyzed epoxidation[40] utilizing the C5 hydroxyl group as a directing unit to furnish the bis-epoxide **55** (61% yield of a 4.3:1 mixture of diastereomers in favor of the desired product). Finally, selective methylation of the C5 alcohol moiety by using a slight modification of Corey's procedure[14] resulted in a 40% yield of (±)-**5**, and a 40% yield of recovered starting material. Although the selectivity in the side-chain epoxidation could benefit from improvement, Sorensen's 11-step sequence stands out as a very concise and efficient synthesis of racemic **5**.

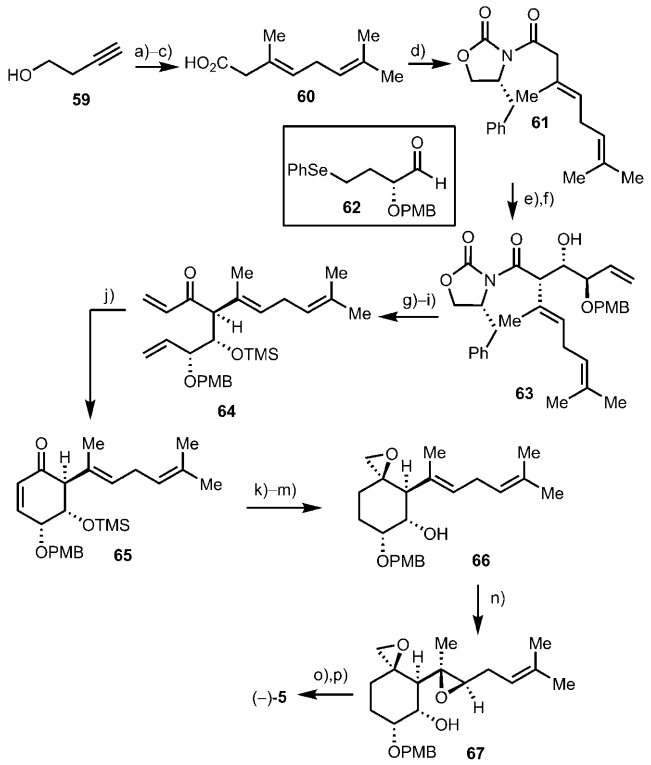
Sorensen and co-workers also reported the asymmetric synthesis of (−)-**5** in 2003 (Scheme 5).[16b] The key step in the synthesis of (−)-**5** is a Diels–Alder reaction that utilizes a diene containing a chiral oxazolidinone auxiliary. Stevenson's chiral diene **56**, prepared from the corresponding oxazolidinone and crotonaldehyde,[42] was treated with acrolein



Scheme 5. Sorensen's synthesis of (−)-**5**. Reagents and conditions: a) acrolein, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 99 %; b) OsO_4, NMO, *i*PrOH, 25 °C, 72 %; c) TsOH, acetone, 23 °C, 83 %; d) 0.5 N NaOH, THF, 23 °C, 76 %.

in the presence of stoichiometric $BF_3{\cdot}OEt_2$ to give the *endo*-cycloadduct **57** as the single isomer in nearly quantitative yield. OsO_4-mediated dihydroxylation of **57** stereoselectively afforded the corresponding diol, which was then converted into acetonide **58** in 60 % overall yield. β-Elimination of the chiral auxiliary then produced the enantiopure aldehyde **46** in 76 % yield. Additionally, the chiral auxiliary can be recovered and recycled. This enantiopure aldehyde could then be used in the reaction sequence shown in Scheme 4, resulting in the asymmetric synthesis of (−)-**5** in a total of 14 steps from crotonaldehyde.

Eustache's synthesis:[19] In 2001, the group of Eustache reported the third asymmetric synthesis of **5** by using a strategy that differed from those of their predecessors (Scheme 6). Their key steps involved the Evans aldol reaction to construct the C4 and C5 stereocenters and ring-closing metathesis (RCM) to form the six-membered ring. Their synthesis commenced with treatment of but-3-yn-1-ol (**59**) with $[ZrCp_2Cl_2]$ and $AlMe_3$, followed by a Negishi coupling with 1-bromo-3-methylbut-2-ene, to give (*E*)-isogeraniol, the desired primary alcohol, but also with the formation of a positional isomer. When the mixture was subjected to Wacker oxidation conditions, only the positional isomer was oxidized, which was easily removed from (*E*)-isogeraniol. The carboxylic acid **60** was obtained from (*E*)-isogeraniol by treatment with CrO_3 in acidic medium in 23 % overall yield.[19] The yield for this sequence is low due to byproduct formation, but fortunately, the desired material could be easily separated. After condensation of carboxylic acid **60** with the chiral oxazolidinone moiety, *N*-acyloxazolidinone (**61**) was deprotonated with LDA and treated with aldehyde **62**, which contained a phenylselenyl group as a masked double bond (prepared from (*R*)-(+)-α-hydroxybutyrolactone in three steps), to afford the *syn*-aldol product **63** as a single isomer. Straightforward transformation of alcohol **63** to the corresponding Weinreb amide[43] was achieved by using $AlMe_3$; subsequent TMS protection of the secondary alcohol and addition of a vinyl Grignard reagent afforded the divinyl species **64**. RCM was effected by using the Grubbs first-generation catalyst[44] in the presence of $[Ti(OiPr)_4]$, resulting in the formation of cyclohexenone **65** (53 % yield). After olefin hydrogenation by using Raney Ni, compound **66** was then produced by spiroepoxide formation

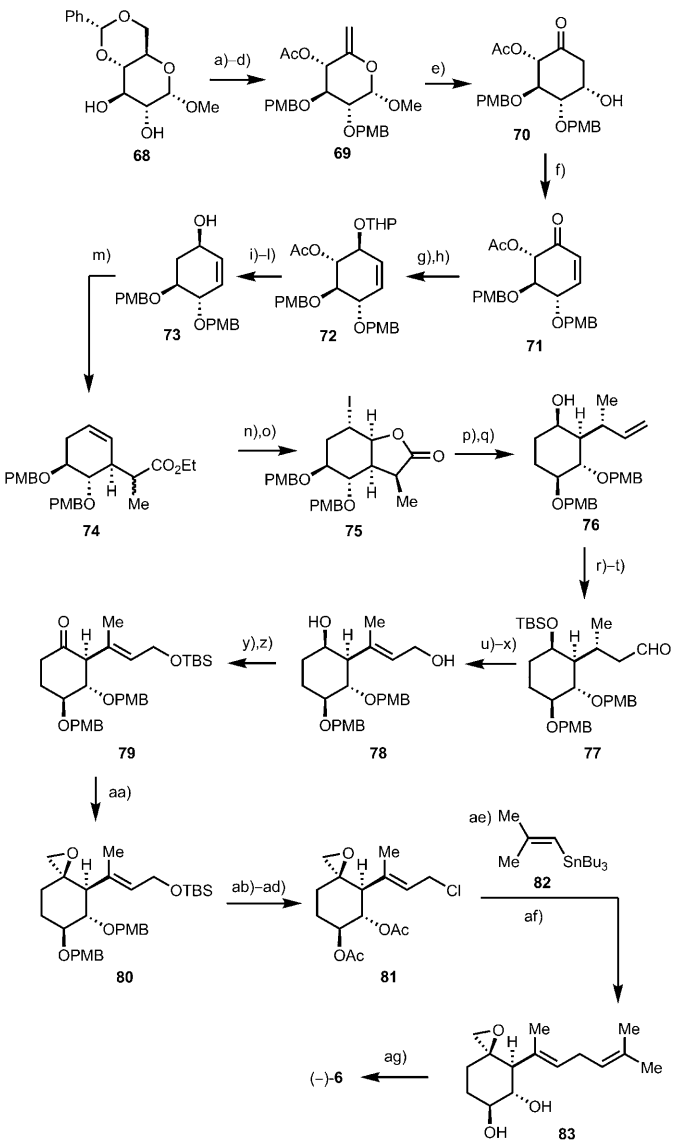


Scheme 6. Eustache's synthesis of (−)-**5**. Reagents and conditions: a) $[ZrCp_2Cl_2]$, $AlMe_3$, DCE, 20 °C; then 1-bromo-3-methyl-but-2-ene, $[Pd(PPh_3)_4]$ (1 mol %), 20 °C; b) CuCl, O_2, $[PdCl_2(CH_3CN)_2]$ (10 mol %), DMF/water (9:1), 30 °C; c) separation, CrO_3, H_2SO_4, H_2O/acetone, 0 °C, 23 % over three steps; d) PivCl, NEt_3, −78 to 0 °C then (*R*)-4-benzyl-2-oxazolidinone lithium salt, −78 °C, 70 %; e) LDA, −78 °C then **62**, −78 °C; f) Bu_4NIO_4, $CHCl_3$, reflux, 55 % over two steps; g) *N*,*O*-dimethylhydroxylamine, $AlMe_3$, THF, 20 °C, 71 %; h) TMSCl, NEt_3, DMAP, THF, 20 °C, 100 %; i) vinylmagnesium bromide, THF, 20 °C, 87 %; j) $[Ti(OiPr)_4]$, the Grubbs first generation catalyst (20 mol %), CH_2Cl_2, 55 °C, 53 %; k) Raney Ni, THF, 0 °C, 83 %; l) $Me_3S^+OI^-$, NaH, LiI, DMSO/THF, 20 °C, 53 %; m) TsOH, H_2O/THF, 75 %; n) $[Ti(OiPr)_4]$, *t*BuOOH, CH_2Cl_2, −25 °C, 65 % (a 1:1 mixture of diastereomers); o) MeI, NaH, THF/DMF (1:1), 20 °C, 97 %, then SiO_2 separation; p) DDQ, CH_2Cl_2/H_2O, 20 °C, 83 %. Cp = cyclopentadienyl, DCE = 1,2-dichloroethane, Piv = pivaloyl, LDA = lithium diisopropylamide, PMB = *p*-methoxybenzyl, DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

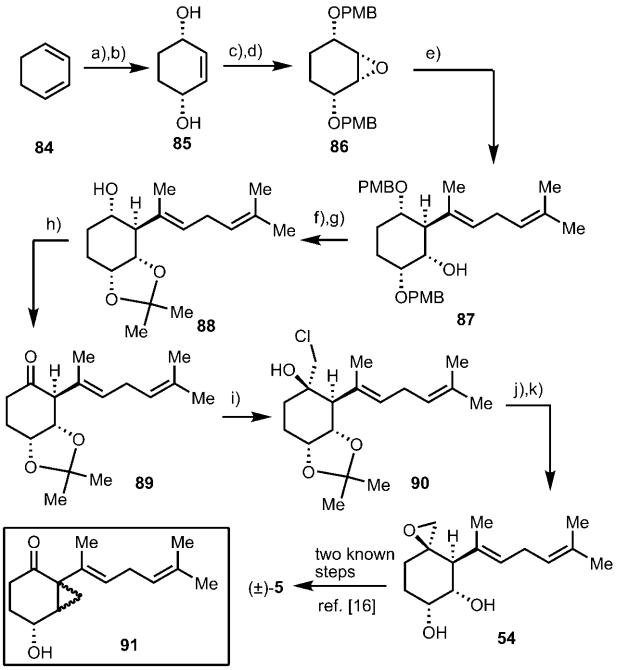
with the Corey–Chaykovsky reagent (dimethylsulfoxonium methylide), followed by TMS deprotection. Had Eustache and co-workers chosen to remove the PMB group at this stage, they would have produced compound **54** from Sorensen's route, and would have completed a formal synthesis of **5**. They instead attempted the epoxidation of the side chain without PMB removal, which proceeded smoothly by using $[Ti(OiPr)_4]$/TBHP;[45] unfortunately, the bis-epoxide **67** was produced as a mixture of inseparable diastereomers in a 1:1 ratio. Methylation of the C5 hydroxyl group in the following step gave diastereomers that were separable. Finally, the PMB protecting group was removed from the desired diastereomer by use of DDQ to give (−)-**5** in good yield. Eustache and co-workers, thus, accomplished the asymmetric total synthesis of (−)-**5** in 16 steps from **59**.

Chida's FR65814 and fumagillol syntheses:[20] The first asymmetric total synthesis of **6**, a fumagillol analogue, was achieved by Chida's group in 1998 (Scheme 7). Their synthesis utilized a modified, catalytic Ferrier rearrangement, which was developed by their own group in 1991.[46] Commercially available **68**, a derivative of D-glucose, was sensibly chosen as their starting material and was converted to **69** in four steps.[47] $Hg(OTf)_2$-mediated, catalytic Ferrier rearrangement of enol ether **69** proceeded smoothly, and β elimination of the resulting alcohol **70** afforded enone **71** in 84% yield over two steps. Reduction of **71** with $NaBH_4$ and $CeCl_3$ produced the corresponding alcohol as a single diastereomer, which was protected as its THP ether **72**. Deacetylation and removal of the revealed hydroxyl group by using the Barton–McCombie deoxygenation,[48] followed by deprotection of the THP group, afforded allylic alcohol **73**. Johnson–Claisen rearrangement[49] of **73** with triethyl orthopropionate at 140°C successfully introduced the C4 stereocenter of **6** stereoselectively to give the γ,δ-unsaturated ester **74** in 74% yield. Although **74** was obtained as an inseparable mixture of diastereomers (1:1 ratio), ester saponification followed by iodolactonization afforded iodolactone **75** as a single isomer. After free-radical removal of the iodine atom, DIBAL-H reduction of the lactone moiety gave the corresponding lactol, which was converted into **76** by a Wittig olefination. TBS protection of alcohol **76**, and subsequent hydroboration of the terminal olefin gave a primary alcohol, which was then oxidized to aldehyde **77**. Conversion to the α,β-unsaturated aldehyde by Ito–Saegusa oxidation,[50] aldehyde reduction with DIBAL-H, and desilylation by using TBAF gave allylic alcohol **78**. The primary alcohol moiety in **78** was then selectively protected as its TBS ether, and oxidation of the secondary alcohol gave ketone **79**. Treatment of **79** with the Corey–Chaykovsky reagent generated spiroepoxide **80** in 57% yield as a single diastereomer. Removal of the PMB groups with DDQ, diol bisacetylation, and desilylation gave the corresponding allylic alcohol, which was then converted to allyl chloride **81** by treatment with MsCl in the presence of LiCl. Stille coupling of chloride **81** with vinylstannane **82**, under $[Pd(PPh_3)_4]$ catalysis provided the coupled product, which was deacetylated to provide diol **83** in 68% yield (over two steps). Finally, epoxidation of **83** was effected by $[VO(acac)_2]$ (10 mol%) and TBHP, giving rise to (−)-**6** in 70% yield (less than 5% of the other isomer was isolated). This first total synthesis of (−)-**6** confirmed the assigned structure and determined its absolute configuration. A few years later, Chida's group also reported the formal total synthesis of **5** by using similar key reactions.[20c]

Simpkins' synthesis:[17] In 2001, Simpkins and co-workers described a short, formal synthesis of racemic **5**, which proceeded with the ring-opening of a symmetrical epoxide intermediate (Scheme 8). The synthesis commenced by converting 1,3-cyclohexadiene (**84**) into epoxide **86** by using the palladium-catalyzed 1,4-diacetoxylation method developed by Bäckvall et al.[51] Thus, oxidation of **84** led to 1,4-diacet-



Scheme 7. Chida's synthesis of (−)-FR65814 (**6**): Reagents and conditions a) NaH, PMBCl, DMF, 0 to 23°C; b) AcOH/H_2O (4:1), 60°C, 85% over two steps; c) Ph_3P, I_2, imidazole, toluene, 23°C, 93%; d) KO*t*Bu, THF, 23°C; then Ac_2O, pyridine, 23°C, 77%; e) $Hg(OTf)_2$ (5 mol%), acetone/H_2O (2:1), 23°C; f) MsCl, Et_3N, CH_2Cl_2, 0°C, 84% over two steps; g) $NaBH_4$, $CeCl_3$·$7H_2O$, MeOH, 0°C, 90%; h) DHP, PPTS, CH_2Cl_2, 23°C, 99%; i) MeONa, MeOH, 23°C; j) NaH, CS_2, imidazole, THF, 0°C; then MeI; k) *n*Bu_3SnH, AIBN, toluene, reflux, 63% over three steps; l) PPTS, EtOH, 50°C, 96%; m) $CH_3CH_2C(OEt)_3$, $CH_3CH_2CO_2H$, 140°C, 74%; n) KO*t*Bu, DMSO, 23°C; o) I_2, KI, THF, $NaHCO_3$ (aq), 23°C; p) *n*Bu_3SnH, AIBN, benzene, reflux, 80% over two steps; q) DIBAL-H, toluene, −78°C; then Ph_3PCH_3Br, *n*BuLi, THF, 60°C, 90%; r) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C; s) BH_3·THF, THF, 0°C; then H_2O_2, NaOH (aq), 0°C, 85%; t) TPAP, NMO, 4 Å MS, CH_2Cl_2, 23°C, 81%; u) KHMDS, THF, 0 to 23°C; then TMSCl, NEt_3, 23°C; v) $Pd(OAc)_2$, CH_3CN, 0°C, 45% over two steps; w) DIBAL-H, toluene, −78°C; x) TBAF, THF; y) TBSCl, imidazole, DMF; z) DMSO, Ac_2O, 82% over four steps; aa) $Me_3S^+OI^-$, NaH, DMSO, 23°C, 57%; ab) DDQ, CH_2Cl_2–H_2O; ac) Ac_2O, pyridine; then TBAF, THF, 90% over two steps; ad) MsCl, LiCl, collidine, DMF, 23°C, quant; ae) compound **82**, $[Pd(PPh_3)_4]$, THF, 40°C, 72%; af) NaOMe, MeOH, 95%; ag) $[VO(acac)_2]$, *t*BuOOH, CH_2Cl_2, −18°C, 70%. OTf = trifluoromethane sulfonate, DHP = 3,4-dihydro-2*H*-pyran, THP = tetrahydropyranyl, PPTS = pyridinium *p*-toluenesulfonate, AIBN = 2,2′-azo bis(isobutyronitrile), TPAP = tetrapropylammonium perruthenate, MS = molecular sieves.

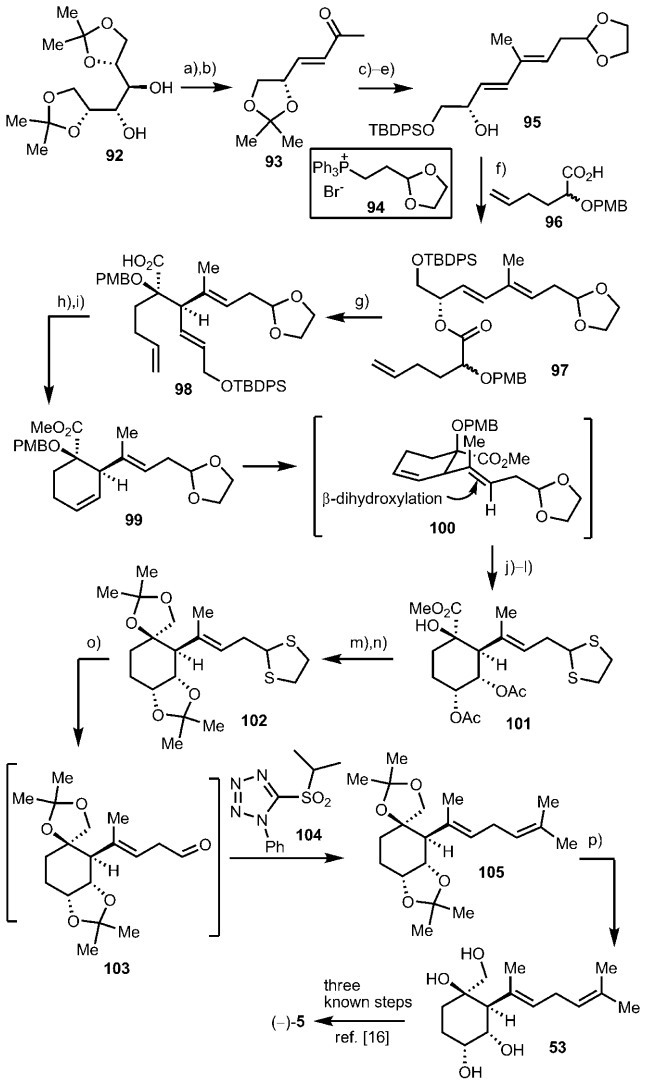


Scheme 8. Simpkins' synthesis of (±)-**5**. Reagents and conditions: a) $Pd(OAc)_2$, LiCl, LiOAc, MnO_2, benzoquinone, AcOH, pentane, 93%; b) K_2CO_3, MeOH, 43%; c) *m*CPBA, EtOAc, Et_2O, 67%; d) NaH, PMBCl, 85%; e) compound **47**, Li(2-thienyl)CuCN, 23°C, 70%; f) NH_3, Na, *t*BuOH, 91%; g) 2,2-dimethoxypropane, PPTS, acetone, 92%; h) Swern or Dess–Martin conditions, 73–77%; i) $ClCH_2I$, *n*BuLi, 64%, (d.r. 16:1 in favor of desired diastereomer); j) 2N HCl, THF, 23°C; k) NaOH, EtOH, 70%, 23°C, over two steps.

oxycyclohex-2-ene, which was then converted into symmetrical epoxide **86** through acetate removal, olefin epoxidation, and PMB protection. The epoxide moiety in **86** was opened by addition of a cuprate reagent (prepared by treatment of **47** with (2-thienyl)cyanocuprate) at room temperature to afford alcohol **87** in 70% yield. Although the reductive removal of the PMB groups of **87** was inefficient with standard methods, such as DDQ and CAN, it proceeded smoothly under Birch conditions. The resulting triol was then converted into acetonide **88** (84% yield) and oxidized by using Swern or Dess–Martin conditions to give ketone **89**. Although **89** was similar to Eustache's and Chida's intermediates (**65** and **79**, respectively), Corey–Chaykovsky epoxidation was not successful, since cyclopropane **91** was produced instead. To obtain the desired epoxide, a less direct route was required. Ketone **89** was, hence, treated with chloromethyllithium as described by Sadhu and Matteson,[52] to afford the chlorohydroxy compound **90** in 64% yield with high diastereoselectivity (d.r. 16:1). Removal of the acetal moiety of compound **90** gave rise to the corresponding diol, which upon treatment with base underwent spiroepoxide formation to afford **54**. This spiroepoxide **54** was identical in all respects to compound **54** described by Sorensen,[16] and therefore the group of Simpkins had achieved the formal total synthesis of racemic **5**, in a total of 13 steps. Although their achievement was a formal synthesis, it represents one of the shortest syntheses to access **5**. If the epoxide opening reaction at the early stages of the synthesis could be rendered asymmetric, a concise asymmetric total synthesis of **5** would be realized.

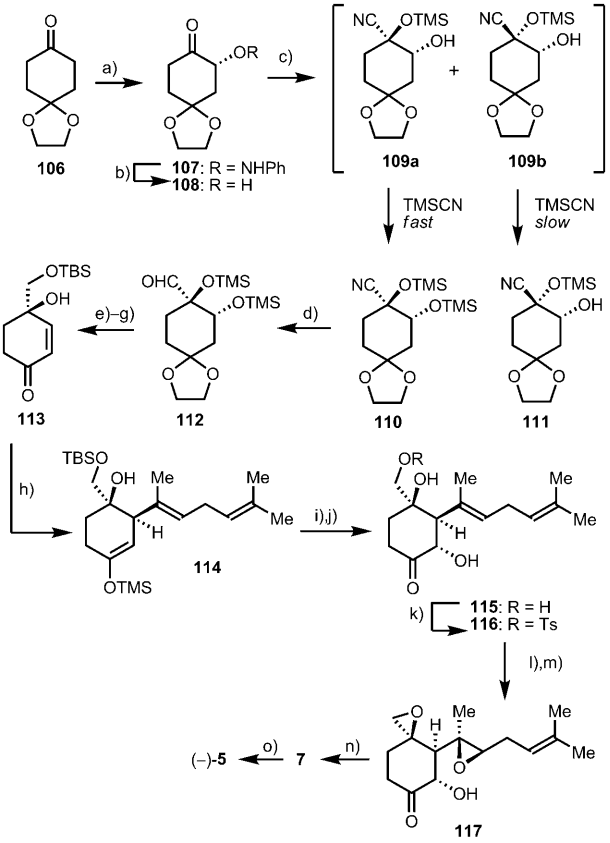
Langlois' synthesis:[21] The Langlois group reported two communications outlining their synthetic studies towards **5** in 1999 and 2003, and finally, in 2004 a formal synthesis of **5** was realized. Key steps in their strategy involved the Ireland–Claisen rearrangement, RCM, and Julia–Kocienski olefination,[53] as shown in Scheme 9. The starting material, diisopropylidenemannitol (**92**), was converted into ketone **93** by using a known sequence of reactions.[54] Wittig olefination of **93** by using the protected phosphonium bromide **94** afforded the (*E*,*E*)-diene in 70% yield. Selective removal of the more labile acetal group, followed by TBDPS monoprotection of the resulting diol gave alcohol **95**, which was then condensed with carboxylic acid **96** by using DCC and DMAP to afford ester **97**. Ireland–Claisen rearrangement of **97** produced γ,δ-unsaturated acid **98**, which was subsequently treated with the Grubbs first-generation catalyst followed by diazomethane to give methyloxycarbonyl cyclohexene **99** in good yield (70% over three steps). Treatment of **99** with the Sharpless dihydroxylation protocol,[55] namely, AD-mix-α and methanesulfonamide in *t*BuOH/H_2O, led to dihydroxylation from the β-face (see conformation in **100**) to afford the desired diol in an acceptable yield (50%). After bis-acetylation of the diol, the acetal moiety was exchanged for a thioacetal, to give **101**, which resulted from a concomitant PMB group cleavage under the acidic reaction conditions. Treatment of ester **101** with $LiAlH_4$ reduced the methyl ester and simultaneously removed the two acetyl groups to produce the corresponding tetraol, which was then treated with dimethoxypropane under acidic conditions to furnish bis-acetonide **102**. Dithioacetal cleavage by using HgO and $HgCl_2$ in water, followed by treatment with KI gave aldehyde **103**, which was immediately treated with sulfonyltetrazole **104** to induce a Julia–Kocienski olefination, affording diene **105**. Finally, the bis-acetonide was removed under acidic conditions, to give tetraol **53**, an intermediate in Sorensen's synthesis of **5**. Tetraol **53** had previously been converted into **5** in three steps,[16] and, thus, Langlois' group accomplished the formal synthesis of (−)-**5** in a total of 19 steps.

Hayashi's synthesis:[22] In 2006, we reported a concise synthesis of **5** and the related compounds RK-805 (**7**) and FR65814 (**6**) by utilizing a proline-catalyzed asymmetric α-aminoxylation methodology[31] developed in our group (Scheme 10). The α-aminoxylation reaction between the cyclohexanone derivative **106** and nitrosobenzene proceeded at 0°C in the presence of proline (10 mol%) in DMF to give the aminoxylated product **107** in 93% yield and with >99% enantiomeric excess (*ee*). Hydrogenolysis of the N–O bond produced hydroxycyclohexanone **108**, which was then converted into **110** by treatment with TMSCN and catalytic Et_3N with high diastereoselectivity (d.r. >95:5).[57] Al-



Scheme 9. Langlois' synthesis of (−)-**5**. Reagents and conditions: a) $NaIO_4$; b) $(MeO)_2P(O)CH_2COCH_3$, >95% over two steps; c) compound **94**, *n*BuLi, THF, −78 to 23°C, 70%; d) AcOH, TFA, 0°C, 78% (15% recovered starting material); e) TBDPSCl, NEt_3, DMAP, THF, 0°C, 82%; f) compound **96**, DCC, DMAP, CH_2Cl_2, 0 to 23°C, 80%; g) KHMDS, toluene, −78°C; then TMSCl, 23°C; h) the Grubbs first generation catalyst (10 mol%), CH_2Cl_2, 40°C; i) CH_2N_2, 70% over three steps; j) AD-mix α, $MeSO_2NH_2$, *t*BuOH/H_2O/acetone, 23°C, 50% (25% recovered starting material); k) Ac_2O, DMAP, pyridine, CH_2Cl_2, 23°C, 86%; l) ethanedithiol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 23°C, 95%; m) $LiAlH_4$, THF, 0°C; n) 2,2-dimethoxypropane, CSA, 23°C, 79% over two steps; o) HgO, $HgCl_2$, acetone/H_2O, KI, 23°C; then **104**, LHMDS, THF, −78°C, 42%; p) HCl, THF–H_2O, 23°C, 71%. TFA = trifluoroacetic acid, CSA = camphorsulfonic acid.

though the diastereofacial selectivity of the cyanide attack onto the prochiral carbonyl group was low (thus giving rise to both **109a** and **109b**), the rates of addition of the second TMS group differed such that the reaction products were primarily the desired product **110** and the mono-TMS ether **111**. The reduction of **110** was accomplished with two successive treatments of DIBAL-H to afford the primary alcohol through the isolable intermediacy of aldehyde **112**. After



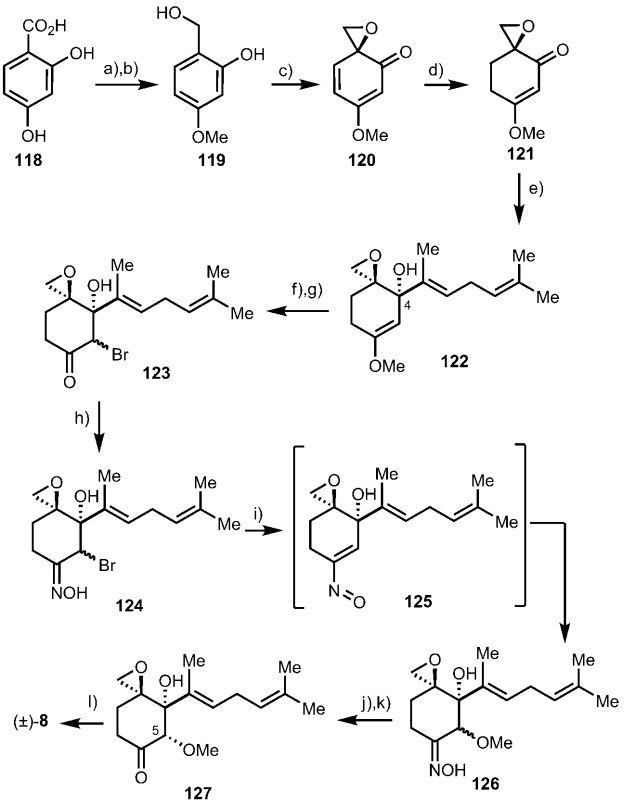
Scheme 10. Hayashi's syntheses of (−)-**5**, FR65814 (**6**), and RK-805 (**7**). Reagents and conditions: a) nitrosobenzene, L-proline, DMF, 0°C, 93%, >99% *ee*; b) Pd/C, H_2, THF, 23°C, 90%; c) TMSCN, cat. NEt_3, CH_2Cl_2, 0°C, 68% (d.r. > 95:5); d) DIBAL-H, Et_2O, −60 to −30°C, 72%; e) DIBAL-H, CH_2Cl_2, 0°C; f) Amberlyst-15, THF, H_2O, 60°C; then silica gel; g) TBSCl, NEt_3, DMAP, CH_2Cl_2, 57% over three steps; h) compound **47**, Me_2Zn, −78 to −40°C; then TMSCl/NEt_3, −40 to −20°C, 61% (d.r. > 95:5); i) DMDO/acetone, MeOH, −90°C; j) TBAF, THF, 23°C, 74%, over two steps (d.r. > 95:5); k) TsCl, NEt_3, DMAP, CH_2Cl_2, 23°C, 71%; l) [VO(acac)$_2$], *t*BuOOH, CH_2Cl_2, 0°C; m) K_2CO_3, MeOH, 0°C, 75% over two steps (d.r. > 95:5); n) MeI, Ag_2O, 23°C, 75%; o) K-selectride, THF, −78°C, 94% (d.r. > 95:5). DMDO = dimethyldioxirane.

acid-induced deprotection of the ketal and silyl groups and elimination of the resulting secondary alcohol, the primary alcohol was protected as a TBS ether to yield enone **113** (41% over four steps). Diastereoselective conjugate addition of side-chain **47** was achieved by generating the vinyl zincate reagent[57] with Me_2Zn, and was followed by TMS trapping to give silyl enol ether **114**. Taber and co-workers[18] reported that a congener of **113** with an acetonide protecting the primary and tertiary hydroxyl units (i.e., compound **38**, Scheme 3) reacted stereoselectively with a vinyl cuprate in an anti sense to the tertiary hydroxyl group, that is, in the undesired fashion. To overcome this inversion of configuration at C3, the group of Taber employed several additional steps to rectify the stereochemistry. In our synthetic route, direct introduction of the side chain with the correct stereochemistry was realized by exploiting the free hydroxyl group in combination with the use of an organozincate reagent, thus rendering the overall synthesis more efficient. Epoxida-

tion of silyl enol ether **114** with DMDO at low temperature (−90 °C) proceeded diastereoselectively without oxidation of the other trisubstituted double bonds; subsequent treatment with TBAF generated α-hydroxycyclohexanone **115** as a single isomer in 74% yield over two steps. Tosylation then selectively converted the primary alcohol into a leaving group to give **116** in 71% yield. To obtain a high degree of stereoselectivity for the epoxidation of the side chain, the order of the next two events was crucial. Excellent diastereoselectivity (d.r. > 95:5) resulted from the epoxidation of dihydroxy tosylate **116** with TBHP and $[VO(acac)_2]$, and bis-epoxide **117** was obtained as a single isomer after treatment with K_2CO_3 in MeOH; however, reversal of the order of the reaction sequence led to low diastereoselectivity (d.r. 2:1). This difference in selectivity is attributed to the restriction of rotational freedom of the bond linking the cyclohexane to the side chain. Having a bulky quaternary center at C3 locks the conformation at the nearest olefin of the side chain, allowing the C5 hydroxyl group to smoothly direct the epoxidation; however, with a less bulky epoxide unit at C3, C4 is less crowded, and, hence, allows side-chain mobility that is detrimental to the diastereoselectivity. Formation of the methyl ether with MeI and Ag_2O in CH_3CN then gave **7**, which was stereoselectively reduced with K-selectride to give **5** as a single isomer in excellent yield (94%). When hydroxyketone **117** was reduced with $NaBH_4$ in MeOH, FR65814 (**6**) was obtained as the major product in 62% yield. To this end, we accomplished concise enantio- and diastereoselective total syntheses of **5**, **6**, and **7** in 14 or 15 steps. It is also of note that this achievement represents the first catalytic asymmetric synthesis of (−)-**5**.

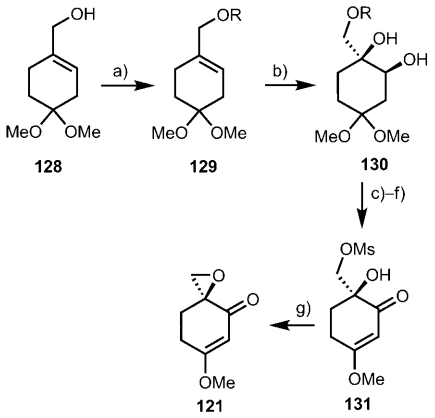
Total Synthesis of Ovalicin and 5-Demethylovalicin

Corey's ovalicin synthesis:[25] Twelve years after accomplishing the first total synthesis of **1**, Corey's group reported the first total synthesis of **8**, by using an approach that differed greatly from that used for **1** (Scheme 11). Starting from 2,4-dihydroxybenzoic acid (**118**), selective simultaneous methylations of the carboxylic acid and the 4-hydroxy unit, followed by Red-Al reduction afforded phenol **119**. Treatment with $NaIO_4$ led to oxidation of the free phenol to provide epoxide **120**. Selective hydrogenation of the γ,δ-olefin **120** by catalytic hydrogenation under various conditions resulted in the formation of phenol **119**. However, the reduced product was ultimately obtained by diimide reduction by using potassium azodicarboxylate and acetic acid at 45 °C to give **121**. The characteristic side chain of this family of natural products was then introduced by using organolithium reagent **47**; treatment of epoxyenone **121** with **47** gave alcohol **122** in 83% yield (d.r. 10:1). Bromination with NBS in methanol led to bromoketal in nearly quantitative yield. After ketal removal by using TsOH, the ketone **123** was converted to oxime **124** to allow for the introduction of a methoxy unit at C5. Treatment of **124** with NEt_3 produced the nitroso compound **125**, which underwent nucleophilic addition of methanol to give methoxyoxime **126**. Oxime hydrolysis with a solution of titanium trichloride yielded the ketone **127** as a 1:1 diastereomeric mixture at C5, which could be isomerized with K_2CO_3 in MeOH to give the desired diastereomer as a single product. Epoxidation of the side chain with $[VO(acac)_2]$ and TBHP proceeded in good yield (89%), thus completing the first synthesis of racemic **8**. This synthesis is short with regard to step count (11 steps), is highly diastereoselective, and includes an interesting transformation to enable the introduction of a methoxy group by a nitroso-Michael reaction. Furthermore, the method of side-chain addition (involving vinyllithium species **47**) that Corey developed has since been used by Sorensen, Simpkins, Samadi, Pollini, Takahashi, Hayashi, Mulzer, and Yadav in their respective syntheses of **5** and **8**.

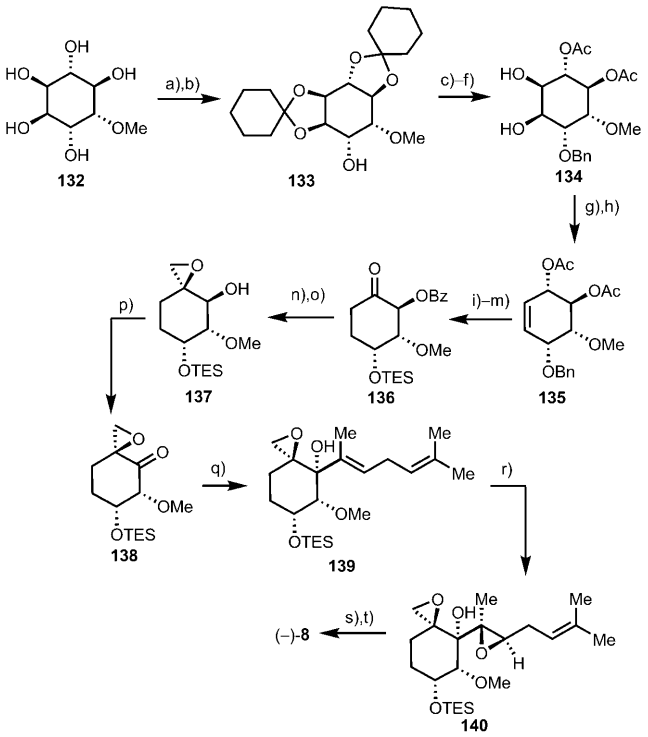


Scheme 11. Corey's first total synthesis of (±)-**8**. Reagents and conditions: a) MeI, K_2CO_3, reflux, 83%; b) Red-Al, Et_2O, reflux, 97%; c) $NaIO_4$, THF/H_2O, 23 °C, 61%; d) potassium azodicarboxylate, AcOH, DME, 45 °C, 77%; e) compound **47**, Et_2O/toluene, −78 °C, 83%; f) NBS, MeOH, 0 °C; g) TsOH, 23 °C, 55% over two steps; h) NH_2OH·HCl, KOAc, AcOH, 23 °C, quant; i) NEt_3, MeOH, 23 °C; j) $TiCl_3$(aq), MeOH, NH_4OAc, 23 °C (d.r. 1:1); k) K_2CO_3, MeOH, 63% over three steps; l) $[VO(acac)_2]$, *t*BuOOH, benzene, 23 °C, 89%. Red-Al = sodium bis-(2-methoxyethoxy)aluminium hydride, NBS = *N*-bromosuccinimide.

In 1994, the group of Corey also reported an effective and simple enantioselective route to chiral intermediate **121** (Scheme 12).[25b] The known allylic alcohol **128**, which was obtained from *p*-methoxybenzyl alcohol in two steps, was bound to an enantioselectivity-enhancing *p*-methoxybenzoyl group to give **129** in 98% yield. Asymmetric dihydroxyla-



Scheme 12. Corey's asymmetric total synthesis of (−)-**8**. Reagents and conditions: a) *p*-methoxybenzoyl chloride, NEt_3, DMAP, 23 °C, 98 %; b) K_2OsO_4, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, *t*BuOH, H_2O, 0 °C, 93 %, >99 % *ee*; c) oxalyl chloride, DMSO, NEt_3, CH_2Cl_2, −78 to 23 °C, 87 %; d) TsOH, CH_2Cl_2, 23 °C, 93 %; e) K_2CO_3, MeOH, 23 °C, 93 %; f) MsCl, NEt_3, CH_2Cl_2, −78 to 23 °C; g) NaOH, 23 °C, 82 % over two steps. R = *p*-methoxybenzoyl.

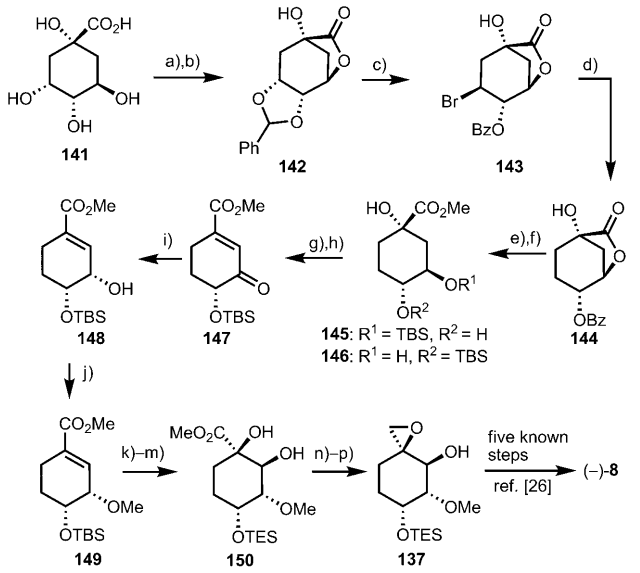


Scheme 13. Samadi's first asymmetric total synthesis of (−)-**8**. Reagents and conditions: a), b) ref. [58]; c) BnBr, DMF, 0 to 23 °C, 90 %; d) ethylene glycol, TsOH, CH_2Cl_2, 23 °C, 70 %; e) Ac_2O, pyridine, 0 to 20 °C, 98 %; f) TFA, THF/H_2O, 23 °C, 77 %; g) $CSCl_2$, DMAP, CH_2Cl_2, 0 °C; h) $(MeO)_3P$, 120 °C; i) NH_3, MeOH, 23 °C, 82 % over three steps; j) MnO_2, CH_2Cl_2, 23 °C, 50 %; k) H_2, Pd/C, 23 °C, EtOH, 94 %; l) BzCl, pyridine, 23 °C, 86 %; m) TESCl, imidazole, DMF, 23 °C, 97 %; n) $Ph_3P{=}CH_2$, THF, −10 to 20 °C, 70 %; o) *m*CPBA, CH_2Cl_2, 0 °C, 84 % (+ 10 % epimer); p) DMSO, TFAA, CH_2Cl_2, −78 to 0 °C, 88 %; q) compound **47**, THF/toluene, −78 °C, 72 %; r) $[VO(acac)_2]$, *t*BuOOH, benzene, 23 °C, 72 % (d.r. 65:35 in favor of the desired diastereomer); s) TBAF, THF; t) PDC, CH_2Cl_2, 23 °C, 78 % over two steps. TFAA = trifluoroacetic anhydride, PDC = pyridinium dichromate.

tion of **129** was achieved by using a mixture of K_2OsO_4, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, and $CH_3SO_2NH_2$ at 0 °C for 4 h to afford diol **130** in 93 % yield and with over 99 % *ee*. In stark contrast, the asymmetric dihydroxylation of allylic alcohol **128** proceeded in a dismal 18 % *ee*, and the same reaction with the pivalate and triisopropylsilyl derivatives of **128** proceeded in only 35 and 13 % *ee*, respectively. Oxidation of the secondary alcohol, elimination of one molecule of MeOH, removal of the enantioselectivity-enhancing ester unit, followed by conversion of the primary alcohol into a mesylate, resulted in hydroxymesylate **131**. Finally, compound **131** was treated with base to yield enantiopure **121**. This work not only provided a strategy for the asymmetric synthesis of **8**, but also described protocols for maximizing enantioselectivity in the dihydroxylation of allylic alcohols.

Samadi's ovalicin synthesis:[26] Samadi and co-workers described the first asymmetric synthesis of (−)-**8** by using chiral-pool-derived L-quebrachitol (**132**) as their starting point (Scheme 13). Pentaol **132** was converted into its protected form **133** following known procedures[58] and subsequent alcohol benzylation. After removal of the more labile *trans*-acetal, the resulting diol was acetylated, and the remaining acetal was then removed to yield differentially protected hexaol **134**. Deoxygenation of the *cis*-diol along with olefination was then successfully achieved by using the Corey–Winter reaction,[59] to afford cyclohexene **135** in 82 % yield over two steps. Treatment of **135** with ammonia removed the acetyl groups, and the resulting allylic alcohol was selectively oxidized by using MnO_2 to give the corresponding enone; hydrogenation of the olefin and concomitant debenzylation, followed by benzoyl and TES protections of the newly released alcohol moieties, gave ketone **136**. Wittig reaction with concomitant removal of the benzoyl group, and subsequent epoxidation with *m*CPBA, gave the desired spiroepoxide **137** as the major isomer (d.r. 89:11). Alcohol oxidation gave epoxyketone **138**, which was then treated with the vinyllithium reagent **47** by using a modification of Corey's procedure to give **139**. Finally, alcohol **139** was stereoselectively epoxidized under Sharpless conditions, and then removal of the TES group followed by PDC oxidation afforded (−)-**8**. The first asymmetric synthesis of (−)-**8** was, thus, achieved by Samadi's group in a total of 20 steps. Although the reactions used in this route are straightforward, some intermediates, notably **138** and **139**, were crucial enough that they were used by Pollini, Takahashi, and Yadav in their respective syntheses of **8**.

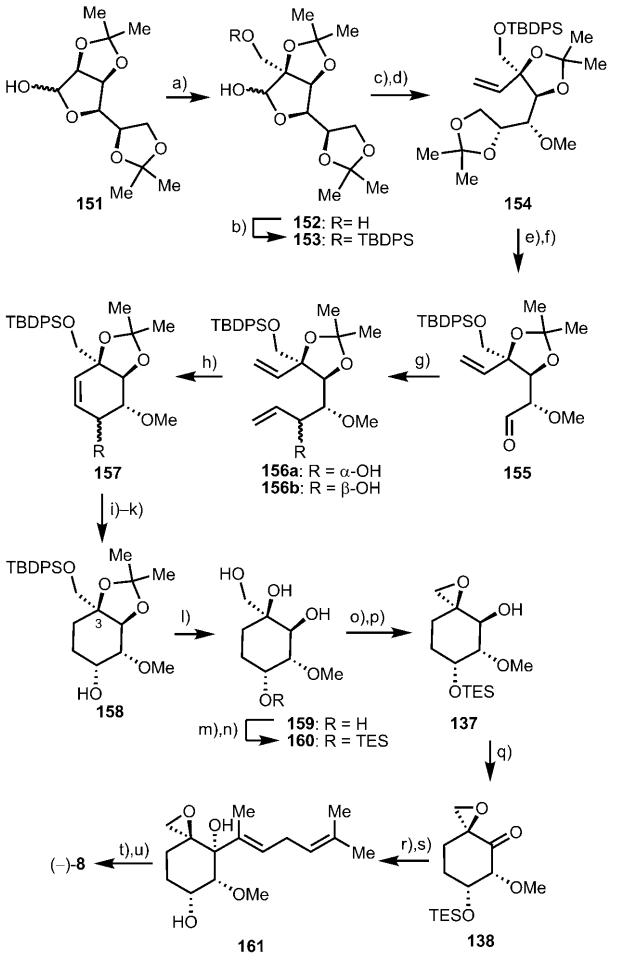
Pollini's ovalicin synthesis:[27] In 1998, the group of Pollini reported a formal, enantioselective synthesis of **8** in which (−)-quinic acid (**141**) was chosen as the starting point (Scheme 14), partially because the Pollini group has had previous experience in the use of **141** as a chiral template for asymmetric synthesis.[60] Bromobenzoate **143** could be generated from **141** in three steps by using previously re-



Scheme 14. Pollini's synthesis of (−)-**8**: Reagents and conditions: a), b) ref. [61]; c) NBS, AIBN, CCl_4, reflux; d) nBu$_3$SnH, AIBN, benzene, reflux, 97%; e) K_2CO_3, MeOH, 0°C, 89%; f) TBSCl, imidazole, DMF, 0 to 23°C, 72%; g) PCC, 3 Å MS, pyridine, CH_2Cl_2, 23°C; h) $POCl_3$, pyridine, 23°C, 60% over two steps; i) $NaBH_4$, MeOH, 0°C, 86%; j) MeI, Ag_2O, CH_2Cl_2, reflux, 88%; k) TBAF, THF, 23°C, 94%; l) TESCl, pyridine, 23°C, 83%; m) OsO_4, NMO, pyridine, H_2O, tBuOH, reflux, 91%; n) $LiAlH_4$, THF, 0°C, 60%; o) TsCl, NEt_3, DMAP, CH_2Cl_2, 0 to 23°C; p) K_2CO_3, MeOH, 23°C, 81% over two steps. PCC = Pyridinium chlorochromate.

ported chemistry.[61] Removal of the bromide under radical conditions afforded **144**,[62] and treatment with K_2CO_3 in MeOH afforded the ring-opened methyl ester. Selective protection of the secondary C5 alcohol was difficult, and mixtures of **145** and **146** were obtained. Gratifyingly, PCC oxidation of the mixture, followed by dehydration, gave enone **147** as the only isolated product in 60% yield over two steps. Carbonyl reduction of **147** then afforded a 4:1 ratio of epimers (favoring the desired isomer), which were separated by silica gel chromatography to yield pure alcohol **148**. Methylation of alcohol **148** then produced methyl ether **149** in good yield (88%). Exchange of the TBS for a TES group, followed by dihydroxylation of **149**, gave diol **150** (71% yield over three steps). The methyl ester was then reduced with DIBAL-H to give the corresponding triol, which was then selectively tosylated and subjected to alkaline conditions to generate spiroepoxide **137** in 48% overall yield. This spiroepoxide is an intermediate in Samadi's synthesis of **8**[26] and would, thus, constitute a formal synthesis, resulting in a 21 step formal sequence to **8**.

Takahashi's synthesis:[28] Takahashi's ovalicin synthesis in 2005 utilized a readily available, chiral-pool-derived D-mannose to construct the complex cyclohexane ring (Scheme 15). The synthesis commenced with regioselective silylation of alcohol **152** (obtained from mannose derivative **151** in 76% yield)[63] to give the silyl-protected species **153** in 85% yield. A Wittig olefination of **153** followed by *O*-

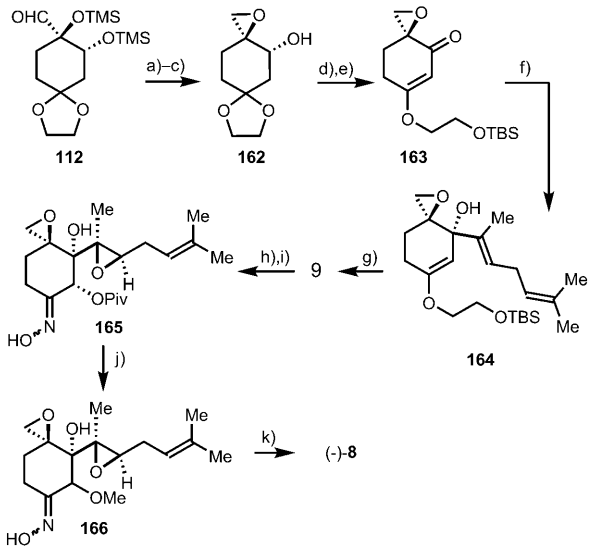


Scheme 15. Takahashi's synthesis of (−)-**8**. Reagents and conditions: a) ref. [63]; b) TBDPSCl, DMAP, NEt_3, CH_2Cl_2, 0 to 23°C, 85%; c) Ph_3PCH_3Br, KOtBu, toluene, 105°C, 97%; d) NaH, MeI, THF, 0°C, 97%; e) AcOH (aq), 50°C, 72%; f) $NaIO_4$, THF/H_2O, 23°C; then ethylene glycol, quant; g) vinylmagnesium chloride, THF, −20°C, 68% for major isomer, 28% for minor isomer; h) the Grubbs second-generation catalyst, toluene, 80°C, 94% from **156b**, 84% from **156a**; i) 10% Pd/C, H_2, EtOAc, 23°C, 99% from major isomer **156b**, 95% from **156a**; j) for the major isomer: DEAD, Ph_3P, benzoic acid, THF, 0 to 23°C; k) NaOMe, MeOH, RT, 95% over two steps; l) HCl, MeOH, 0 to 23°C, 97%; m) TESCl, imidazole, DMF, 0°C, 95%; n) TBAF, THF, −78°C, 87%; o) TsCl, NEt_3, DMAP, CH_2Cl_2, 0 to 23°C; p) K_2CO_3, MeOH, 0°C, 93%; q) DMP, $NaHCO_3$, CH_2Cl_2, 0°C, 98%; r) compound **47**, THF, −78°C, 85%; s) TBAF, THF, 0°C, 90%; t) TPAP, NMO, 4 ÅMS, CH_2Cl_2, 0 to 23°C, 79%; u) [VO(acac)$_2$], tBuOOH, benzene/decane, 0 to 23°C, 64%. DEAD = diethyl azodicarboxylate.

methylation afforded **154** in high yield (94%, two steps). Selective removal of the less hindered acetonide gave a diol that was converted into aldehyde **155** by using $NaIO_4$ (72%, two steps). Treatment of **155** with several vinylating reagents was examined, with the best results giving a 1:2.4 mixture of separable diastereomers **156a** and **156b**, of which the undesired isomer was the major product. The minor isomer, **156a**, underwent RCM to give **157**,[64] which was followed by olefin reduction to provide alcohol **158** (80%, two steps). The major isomer, **156b**, was subjected to the same conditions as the minor isomer, but with an additional two-step

sequence, namely Mitsunobu inversion at the C3 alcohol followed by debenzoylation, to convert the originally undesired material into **158** (88% over four steps). Subsequent removal of the acetonide and TBDPS groups under acidic conditions afforded **159** in excellent yield (97%). Treatment with TESCl introduced three TES groups concurrently (on all but the tertiary alcohol), and upon treatment of this compound with TBAF at −78°C, regioselective desilylation occurred to afford the desired mono-TES ether **160** in 83% yield over two steps. Triol **160** was transformed into spiroepoxide **137** via an intermediate primary tosylate (93%, two steps). Treatment of **137** with DMP in the presence of $NaHCO_3$ furnished Samadi's key intermediate **138**. At this stage, a formal synthesis of **8** had been achieved; however, Takahashi and co-workers completed the total synthesis of (−)-**8** by performing the necessary reactions in an alternative order. After introduction of the side chain by using Samadi's procedure, they removed the TES protecting group before alcohol oxidation and epoxidation of the side chain, thus, completing their 20 step pursuit of **8**.

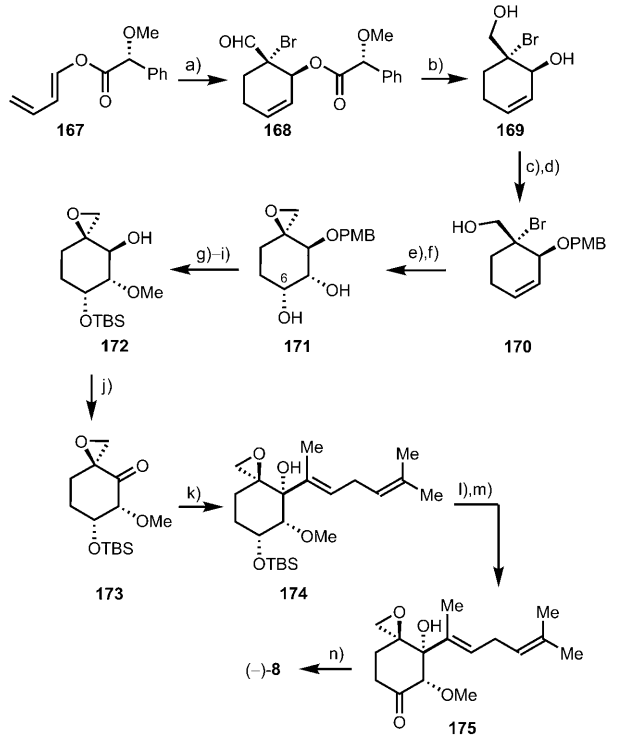
Hayashi's synthesis:[22] When we reported the total synthesis of **5**, we had also disclosed the syntheses of **8** and **9** (Scheme 16). We chose intermediate **112** (Scheme 10) from the fumagillol synthesis as a point of divergence. After formation of spiroepoxide **162**, oxidation with DMP, followed by acidification on silica gel generated the corresponding primary alcohol that was subsequently treated with TBSCl to afford **163**. The characteristic side chain of this natural product family was introduced in a highly diastereoselective



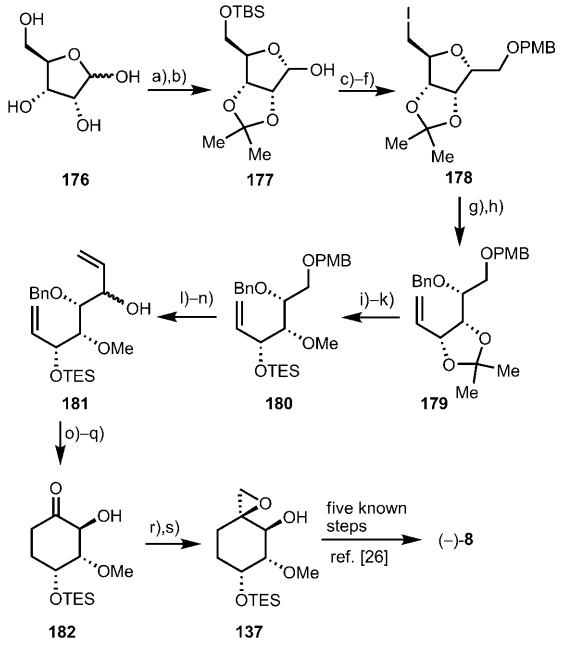
Scheme 16. Hayashi's syntheses of (−)-**9** and (−)-**8**. Reagents and conditions: a) DIBAL-H, CH_2Cl_2, −50 to −30°C; b) MsCl, NEt_3, DMAP, CH_2Cl_2, −40°C; c) K_2CO_3, MeOH, 23°C, 81% over three steps; d) DMP, CH_2Cl_2, 0°C; then silica gel; e) TBSCl, imidazole, DMF, 23°C, 60% over two steps; f) compound **47**, Et_2O/toluene, −78°C, 91%; g) cat. [VO(O*i*Pr)$_3$], *t*BuOOH, −60°C, 64%, single isomer; h) PivCl, NEt_3, DMAP, CH_2Cl_2, 84%; i) NH_2OH·HCl, NEt_3, EtOH, 23°C, 90%; j) K_2CO_3, MeOH, 23°C; k) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 72% over two steps.

manner by using Corey's vinyllithium reagent **47**, giving alcohol **164** in 91% yield. Conventional epoxidation methods, such as [VO(acac)$_2$]/TBHP or *m*CPBA, gave a complex mixture of products due to the instability of the side chain, and DMDO selectively epoxidized the incorrect side-chain double bond; however, [VO(O*i*Pr)$_3$][65] was found to be an efficient catalyst, promoting the epoxidation of both the enol ether and the desired side-chain olefin at low temperature (−60°C), affording **9**. This efficient operation orchestrated the simultaneous creation of three stereogenic centers and gave a single isomer as the reaction product. This selectivity can be attributed to the conformational restriction of the side chain caused by the hydroxyl group at C4, which overpowers the loss in steric bulk that is accompanied by the formation of the epoxide at C3 (see above, Scheme 10). The last remaining task in converting **9** into **8** was the transformation of the alcohol into its methyl ether. Although conventional reagents, such as NaH and MeI, Ag_2O and MeI, or MeOTf and 2,6-di-*tert*-butylpyridine, failed, a modification of the oxime/nitroso strategy used by Corey in his synthesis gave **8** stereoselectively. Thus, protection of the alcohol as its pivalate ester, formation of oxime **165**, treatment with base in MeOH, and conversion of methoxyoxime **166** into a ketone under alkylative conditions, gave **8** as a single isomer (54% over four steps). Ultimately, we were able to achieve the asymmetric syntheses of **9** and **8** in 11 and 15 steps, respectively, through judicious choice of the epoxidation catalyst [VO(O*i*Pr)$_3$], which allowed for diastereoselective double epoxidation that occurred without affecting the second olefin of the side chain. This strategy streamlined the synthesis of these natural products and played an important role in improving its overall efficiency.

Mulzer's synthesis:[29] In 2007, Mulzer's group achieved the total synthesis of **8** by using a Diels–Alder reaction (Scheme 17) that had been previously employed in the synthesis of **1** as outlined in Schemes 1 and 5. They initially examined the Diels–Alder reaction under chiral catalysis, but the enantioselectivity was not sufficient, and they thus resorted to using chiral auxiliaries. Diene **167**, prepared by using the procedure reported by Trost et al.,[66] underwent cycloaddition with α-bromoacrolein in the presence of BF_3·OEt_2 to afford cycloadduct **168** in good yield (75%) and acceptable diastereoselectivity (d.r. 8:1). Removal of the chiral auxiliary by using a borane–ammonia complex gave diol **169** in 89% yield. Benzylidene acetal formation and DIBAL-H reduction were used to selectively protect the secondary alcohol, furnishing bromoalcohol **170** (84%, two steps). After conversion to the corresponding spiroepoxide by using NaH, dihydroxylation with OsO_4 gave diol **171** as a single isomer (90%, two steps). Selective protection of the C6 alcohol, subsequent *O*-methylation and PMB group removal with DDQ, gave alcohol **172** (78%, three steps). The resulting alcohol was oxidized by using DMP to procure intermediate **173**, which only differed from Samadi's and Takahashi's intermediate by the nature of the C6 alcohol protecting group (TBS vs. TES). The desired target,



Scheme 17. Mulzer's synthesis of (−)-**8**. Reagents and conditions: a) α-bromoacrolein, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 75 %; b) $BH_3{\cdot}NH_3$, Et_2O, 23 °C, 89 %; c) *p*-$MeOC_6H_4CH(OMe)_2$, CSA, CH_2Cl_2, 23 °C, 89 % (d.r. 8:1 in favor of the desired isomer); d) DIBAL-H, CH_2Cl_2, −10 to 0 °C, 94 %; e) NaH, THF, MeOH, 0 to 23 °C, 98 %; f) OsO_4, NMO, acetone/H_2O, 23 °C, 92 %; g) TBSCl, imidazole, CH_2Cl_2, 23 °C, 89 %; h) NaH, MeI, THF, 23 °C, 99 %; i) DDQ, CH_2Cl_2, H_2O, 23 °C, 89 %; j) DMP, $NaHCO_3$, CH_2Cl_2, 23 °C, 92 %; k) compound **47**, Et_2O, toluene, −78 °C, 76 %; l) TBAF, THF, 0 °C, 94 %; m) DMP, $NaHCO_3$, CH_2Cl_2, 23 °C, 90 %; n) [$VO(acac)_2$], *t*BuOOH, benzene, 23 °C, 71 %.



Scheme 18. Yadav's synthesis of (−)-**8**. Reagents and conditions: a) 2,2-dimethoxypropane, acetone, TsOH, 23 °C, 72 %; b) TBSCl, imidazole, CH_2Cl_2, 23 °C, 98 %; c) $Me_2SO{=}CH_2$, DMSO, 20 °C, 60 %; d) NaH, PMBBr, Et_2O, 0 to 23 °C, 97 %; e) TBAF, THF, 98 %; f) I_2, PPh_3, imidazole, toluene, reflux, 99 %; g) Zn, EtOH, reflux, 95 %; h) NaH, BnBr, THF, 0 to 23 °C, 85 %; i) TsOH, MeOH, 23 °C, 98 %; j) TESCl, imidazole, 0 °C, 84 %; k) NaH, MeI, THF, 0 to 23 °C, 95 %; l) DDQ, CH_2Cl_2/H_2O (8:2), 23 °C, 61 %; m) TPAP, NMO, CH_2Cl_2, 23 °C, 80 %; n) vinylmagnesium bromide, THF, 23 °C, 75 %; o) the Grubbs first generation catalyst (10 mol %), CH_2Cl_2, 23 °C, 98 %; p) IBX, DMSO, CH_2Cl_2, 23 °C, 69 %; q) $Pd(OH)_2$, THF, H_2, 87 %; r) $MePPh_3I$, *t*BuOK, THF, 0 to 23 °C, 87 %; s) *m*CPBA, CH_2Cl_2, 0 to 23 °C, 85 %. IBX = 2-iodoxybenzoic acid.

(−)-**8**, was thus completed by using a slight modification of Takahashi's procedure.[28] An interesting note, however, is that although Mulzer's group utilized the same vinyllithium species **47**, they had prepared it by an alternative method to Corey's original procedure.[25a,41] Whereas Corey's group made use of a Shapiro reaction and used acetone sulfonylhydrazone to forge **47**, Mulzer's group modified, in a few steps, a vinylstannane that was used in Taber's synthesis[18] (i.e., the desilylated form of **39**), which originally arose from 2,3-dihydrofuran.

Yadav's synthesis:[30] The most recent report is that of Yadav and co-workers, in which a carbohydrate-based approach was used for the formal synthesis of **8** (Scheme 18). D-Ribose (**176**) was chosen as the starting material and was converted into acetonide **177** according to a known procedure.[67] After a one-carbon homologation, PMB protection, and TBS removal, the alcohol was converted into iodide **178**. Zinc-mediated ring-opening of tetrahydrofuran **178** and benzylation of the resulting secondary alcohol gave **179** in good yield (81 %, two steps). After acidic acetal hydrolysis, the allylic alcohol was selectively protected as its TES ether, and the remaining secondary alcohol was methylated to give **180** in 78 % yield over three steps. PMB removal produced a primary alcohol, which was then oxidized to the corresponding aldehyde and treated with a vinyl Grignard reagent to give allylic alcohol **181** (37 % over three steps). The resulting divinyl species was subjected to RCM with the Grubbs first-generation catalyst to afford the cyclohexene product in excellent yield (98 %); oxidation of the allylic alcohol by IBX, followed by hydrogenation of the enone with $Pd(OH)_2$ under an atmosphere of hydrogen gave substituted cyclohexanone **182** (60 %, two steps). Ketone **182** was then subjected to a Wittig olefination followed by epoxidation, resulting in epoxide **137** (74 % yield, two steps). Compound **137** was one of Samadi's synthetic intermediates,[26] and its formation, thus, signified that a formal synthesis of **8** had been achieved (with a total step count of 24).

Conclusion

This review has systematically summarized the existing 16 total syntheses of natural products in the fumagillin and ovalicin family. Although these molecules are relatively small in size, many chemists have endeavored to develop concise, practical, and short routes toward them for over 35

years. The synthetic studies demonstrated, herein, not only display the power of classical and current synthetic methods, but they also exhibit the colorful creativity of the synthetic chemists involved, who all strive to create the same molecule, but often with completely different strategies. Only with a side-by-side comparison of synthetic routes one can truly appreciate the depth of organic synthesis, in both its beauty and its flaws. Synthesizing a previously conquered molecule in an alternative manner and perpetually challenging the work of our predecessors widens chemical horizons, and shall continue to provide valuable learning tools and methods of evolution in the art and science of organic synthesis.

[1] a) J. Folkman, *J. Natl. Cancer Inst.* **1990**, *82*, 4; b) W. Risau, *Nature* **1997**, *386*, 671; c) G. Gasparini, *Drugs* **1999**, *58*, 17; d) M. Cristofanilli, C. Charnsangavej, G. N. Hortobagyi, *Nat. Rev. Drug Discovery* **2002**, *1*, 415; e) R. Kerbel, J. Folkman, *Nat. Rev. Cancer* **2002**, *2*, 727; f) M. Shibuya, *Cell Struct. Funct.* **2001**, *26*, 25.
[2] J. Folkman, *New Engl. J. Med.* **1971**, *285*, 1182.
[3] a) F. R. Hanson, T. E. Elbe, *J. Bacteriol.* **1949**, *58*, 527; b) T. E. Elbe, F. R. Hanson, *Antibiot. Chemother.* **1951**, *1*, 54.
[4] a) D. Ingber, T. Fujita, S. Kishimoto, K. Sudo, T. Kanamaru, H. Brem, J. Folkman, *Nature* **1990**, *348*, 555; b) J. Kwon, H. Jeong, K. Kang, Y. Hang, K. Bae, J. Choi, U. Lee, K. Son, B. Kwon, *Antibiotics* **2000**, *53*, 799.
[5] a) C. I. Hong, J. W. Kim, S. J. Lee, S. K. Ahn, N. S. Choi, R. K. Hong, H. S. Chun, S. K. Moon, C. K. Han, WO Patent 9959986, **1999**; b) C. K. Han, S. K. Ahn, N. S. Choi, R. K. Hong, S. K. Moon, H. S. Chun, S. J. Lee, J. W. Kim, C. I. Hong, D. Kim, J. H. Yoon, K. T. No, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 39.
[6] H. P. Sigg, H. P. Weber, *Helv. Chim. Acta* **1968**, *51*, 1395.
[7] K.-H. Son, J.-Y. Kwon, H.-W. Jeong, H.-K. Kim, C.-J. Kim, Y.-H. Chang, J.-D. Choi, B.-M. Kwon, *Bioorg. Med. Chem.* **2002**, *10*, 185.
[8] a) M. Hayashi, Y. P. Kim, S. Takamatsu, S. Preeprame, T. Komiya, R. Masuma, H. Tanaka, K. Komiyama, S. Omura, *J. Antibiot.* **1996**, *49*, 631; b) S. Takamatsu, Y. P. Kim, T. Komiya, T. Sunazuka, M. Hayashi, H. Tanaka, K. Komiyama, S. Omura, *J. Antibiot.* **1996**, *49*, 635.
[9] a) E. C. Griffith, Z. Su, B. E. Turk, S. Chen, Y. H. Chang, Z. Wu, K. Biemann, J. O. Liu, *Chem. Biol.* **1997**, *4*, 461; b) N. Sin, L. Meng, M. Q. W. Wang, J. J. Wen, W. G. Bornmann, C. M. Crews, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 6099.
[10] Y. Asami, H. Kakeya, R. Onose, Y.-H. Chang, M. Toi, H. Osada, *Tetrahedron* **2004**, *60*, 7085.
[11] Y. Asami, H. Kakeya, G. Okada, M. Toi, H. Osada, *J. Antibiot.* **2006**, *59*, 724.
[12] H. Hatanaka, T. Kino, M. Hashimoto, Y. Tsurumi, A. Kuroda, H. Tanaka, T. Goto, M. Okuhara, *J. Antibiot.* **1988**, *41*, 999.
[13] N. Watanabe, Y. Nishihara, T. Yamaguchi, A. Koito, H. Miyoshi, H. Kakeya, H. Osada, *FEBS Lett.* **2006**, *580*, 2598.
[14] E. J. Corey, B. B. Snider, *J. Am. Chem. Soc.* **1972**, *94*, 2549.
[15] a) D. Kim, S. K. Ahn, H. Bae, W. J. Choi, H. S. Kim, *Tetrahedron Lett.* **1997**, *38*, 4437; b) D. Kim, S. K. Ahn, H. Bae, H. S. Kim, *Arch. Pharm. Res.* **2005**, *28*, 129.
[16] a) D. A. Vosburg, S. Weiler, E. J. Sorensen, *Angew. Chem.* **1999**, *111*, 1024; *Angew. Chem. Int. Ed.* **1999**, *38*, 971; b) D. A. Vosburg, S. Weiler, E. J. Sorensen, *Chirality* **2003**, *15*, 156.
[17] M. Hutchings, D. Moffat, N. S. Simpkins, *Synlett* **2001**, 661.
[18] D. F. Taber, T. E. Christos, A. L. Rheingold, I. A. Guzei, *J. Am. Chem. Soc.* **1999**, *121*, 5589.
[19] J.-G. Boiteau, P. Van de Weghe, J. Eustache, *Org. Lett.* **2001**, *3*, 2737.
[20] a) S. Amano, N. Ogawa, M. Ohtsuka, N. Chida, *Tetrahedron* **1999**, *55*, 2205; b) S. Amano, N. Ogawa, M. Ohtsuka, N. Chida, *Chem. Commun.* **1998**, 1263; c) M. Bouno, H. Imase, N. Ogawa, N. Chida, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **2003**, *45*, 395.
[21] a) W. Picoul, R. Urchegui, A. Haudrechy, Y. Langlois, *Tetrahedron Lett.* **1999**, *40*, 4797; b) W. Picoul, O. Bedel, A. Haudrechy, Y. Langlois, *Pure Appl. Chem.* **2003**, *75*, 235; c) O. Bedel, A. Haudrechy, Y. Langlois, *Eur. J. Org. Chem.* **2004**, 3813.
[22] J. Yamaguchi, M. Toyoshima, M. Shoji, H. Kakeya, H. Osada, Y. Hayashi, *Angew. Chem.* **2006**, *118*, 803; *Angew. Chem. Int. Ed.* **2006**, *45*, 789.
[23] D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127.
[24] a) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1962**, *84*, 867; b) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353.
[25] a) E. J. Corey, J. P. Dittami, *J. Am. Chem. Soc.* **1985**, *107*, 256; b) E. J. Corey, A. Guzman-Perez, M. C. Noe, *J. Am. Chem. Soc.* **1994**, *116*, 12109.
[26] a) S. Bath, D. C. Billington, S. D. Gero, B. Quiclet-Sire, M. Samadi, *J. Chem. Soc. Chem. Commun.* **1994**, 1495; b) D. H. R. Barton, S. Bath, D. D. Billington, S. D. Gero, B. Quiclet-Sire, M. Samadi, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1551.
[27] A. Barco, S. Benetti, C. De Risi, P. Marchetti, G. P. Pollini, V. Zanirato, *Tetrahedron: Asymmetry* **1998**, *9*, 2857.
[28] S. Takahashi, N. Hishinuma, H. Koshino, T. Nakata, *J. Org. Chem.* **2005**, *70*, 10162.
[29] K. Tiefenbacher, V. B. Arion, J. Mulzer, *Angew. Chem.* **2007**, *119*, 2744; *Angew. Chem. Int. Ed.* **2007**, *46*, 2690.
[30] J. S. Yadav, S. Pamu, D. C. Bhunia, S. Pabbaraja, *Synlett* **2007**, 992.
[31] a) Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.* **2003**, *44*, 8293; b) Y. Hayashi, J. Yamaguchi, T. Sumiya, M. Shoji, *Angew. Chem.* **2004**, *116*, 1132; *Angew. Chem. Int. Ed.* **2004**, *43*, 1112; c) Y. Hayashi, J. Yamaguchi, T. Sumiya, K. Hibino, M. Shoji, *J. Org. Chem.* **2004**, *69*, 5966.
[32] J. J. Ritter, T. J. Kaniecki, *J. Org. Chem.* **1962**, *27*, 622.
[33] M. Haga, M. Takano, S. Tejima, *Carbohydr. Res.* **1972**, *21*, 440.
[34] O. Mitsunobu, *Synthesis* **1981**, 1.
[35] For the Burke–Fujisawa–Kallmerten modification of the Ireland–Claisen rearrangement; see: a) S. D. Burke, W. F. Fobare, G. J. Pacofsky, *J. Org. Chem.* **1983**, *48*, 5221; b) T. Sato, K. Tajima, T. Fujisawa, *Tetrahedron Lett.* **1983**, *24*, 729; c) J. Kallmerten, T. J. Gould, *Tetrahedron Lett.* **1983**, *24*, 5177.
[36] D. F. Taber, A. Sahli, H. Yu, R. P. Meagley, *J. Org. Chem.* **1995**, *60*, 6571.
[37] G. M. Rubottom, M. A. Vazquez, D. R. Pelegrina, *Tetrahedron Lett.* **1974**, *15*, 4319.
[38] W. Langenbeck, O. Godde, L. Weschky, R. Schaller, *Ber. Dtsch. Chem. Ges.* **1942**, *75*, 232.
[39] a) C. H. Cummins, R. M. Coates, *J. Org. Chem.* **1983**, *48*, 2070; b) R. M. Coates, C. H. Cummins, *J. Org. Chem.* **1986**, *51*, 1383.
[40] K. B. Sharpless, R. C. Michaelson, *J. Am. Chem. Soc.* **1973**, *95*, 6136.
[41] E. J. Corey, J. Lee, B. E. Roberts, *Tetrahedron Lett.* **1997**, *38*, 8915.
[42] a) J. P. Murphy, M. Nieuwenhuyzen, K. Reynolds, P. K. S. Sarma, P. J. Stevenson, *Tetrahedron Lett.* **1995**, *36*, 9533; b) H. McAlonan, J. P. Murphy, M. Nieuwenhuyzen, K. Reynolds, P. K. S. Sarma, P. J. Stevenson, N. Thompson, *J. Chem. Soc. Perkin Trans. 1* **2002**, *13*, 69.
[43] A. Basha, J. L. Lipton, S. M. Weinreb, *Tetrahedron Lett.* **1977**, *18*, 4171.
[44] P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100.
[45] K. B. Sharpless, T. R. Verhoeven, *Aldrichim. Acta* **1979**, *12*, 63.
[46] N. Chida, M. Ohtsuka, K. Ogura, S. Ogawa, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2118.
[47] a) N. Chida, M. Ohtsuka, K. Nakazawa, S. Ogawa, *J. Org. Chem.* **1991**, *56*, 2976; b) N. Chida, M. Ohtsuka, S. Ogawa, *J. Org. Chem.* **1993**, *58*, 4441; c) N. Chida, M. Jitsuoka, Y. Yamamoto, M. Ohtsuka, S. Ogawa, *Heterocycles* **1996**, *43*, 1385; d) N. Chida, K. Sugihara, S. Ogawa, *J. Chem. Soc. Perkin Trans. 1* **1997**, 275.
[48] D. H. R. Barton, S. W. McCombie, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574.

[49] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brockson, T.-T. Li, D. J. Faulker, M. R. Petersen, *J. Am. Chem. Soc.* **1970**, *92*, 741.
[50] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011.
[51] J. E. Bäckvall, S. E. Bystrom, R. E. Nordberg, *J. Org. Chem.* **1984**, *49*, 4619.
[52] K. M. Sadhu, D. S. Matteson, *Tetrahedron Lett.* **1986**, *27*, 795.
[53] P. J. Kocienski, A. Bell, P. R. Blakemore, *Synlett* **2000**, 365.
[54] a) S. Takano, K. Ogasawara, *Yuki Gosei Kagaku Kyokaishi* **1987**, *45*, 1157; b) S. Ohira, T. Ida, M. Moritani, T. Hasegawa, *J. Chem. Soc. Perkin Trans. 1* **1998**, 293.
[55] E. N. Jacobsen, I. Marko, W. S. Mungall, G. Schroder, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 1968.
[56] S. Kobayasi, Y. Tsuchiya, T. Mukaiyama, *Chem. Lett.* **1991**, 537.
[57] M. Suzuki, Y. Morita, H. Koyano, M. Koga, R. Noyori, *Tetrahedron* **1990**, *46*, 4809.
[58] S. D. Gero, *Tetrahedron Lett.* **1966**, *6*, 591.
[59] a) E. J. Corey, R. A. E. Winter, *J. Am. Chem. Soc.* **1963**, *85*, 2677; b) E. J. Corey, F. A. Carey, R. A. E. Winter, *J. Am. Chem. Soc.* **1965**, *87*, 934.
[60] a) E. Albertini, A. Barco, S. Benetti, C. De Risi, G. P. Pollini, V. Zanirato, *Tetrahedron Lett.* **1997**, *38*, 681; b) E. Albertini, A. Barco, S. Benetti, C. De Risi, G. P. Pollini, V. Zanirato, *Tetrahedron* **1997**, *53*, 17177.
[61] a) P. A. Bartlett, U. Maitra, P. M. Chouinard, *J. Am. Chem. Soc.* **1986**, *108*, 8068; b) J. D. White, J. H. Cammack, K. Sakuma, G. W. Rewcastle, R. K. Widener, *J. Org. Chem.* **1995**, *60*, 3600.
[62] D. Lesuisse, G. A. Berchtold, *J. Org. Chem.* **1985**, *50*, 888.
[63] Z. J. Witczak, R. L. Whistler, J. R. Daniel, *Carbohydr. Res.* **1984**, *133*, 235.
[64] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953.
[65] D. R. Pesiri, D. K. Morita, T. Walker, W. Tumas, *Organometallics* **1999**, *18*, 4916.
[66] B. M. Trost, L. S. Chupak, T. Luebbers, *J. Org. Chem.* **1997**, *62*, 736.
[67] C. Frechou, L. Dheilly, D. Beaupere, R. Uzan, G. Demailly, *Tetrahedron Lett.* **1992**, *33*, 5067.

Published online: March 5, 2010

