Synthesis of (−)-LL-C10037α and Related Manumycin-Type Epoxyquinols

Peter Wipf,*[1] Yuntae Kim, Heike Jahn

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA

Fax +1(412)6240787; E-mail pwipf+@pitt.edu

Received 15 August 1995

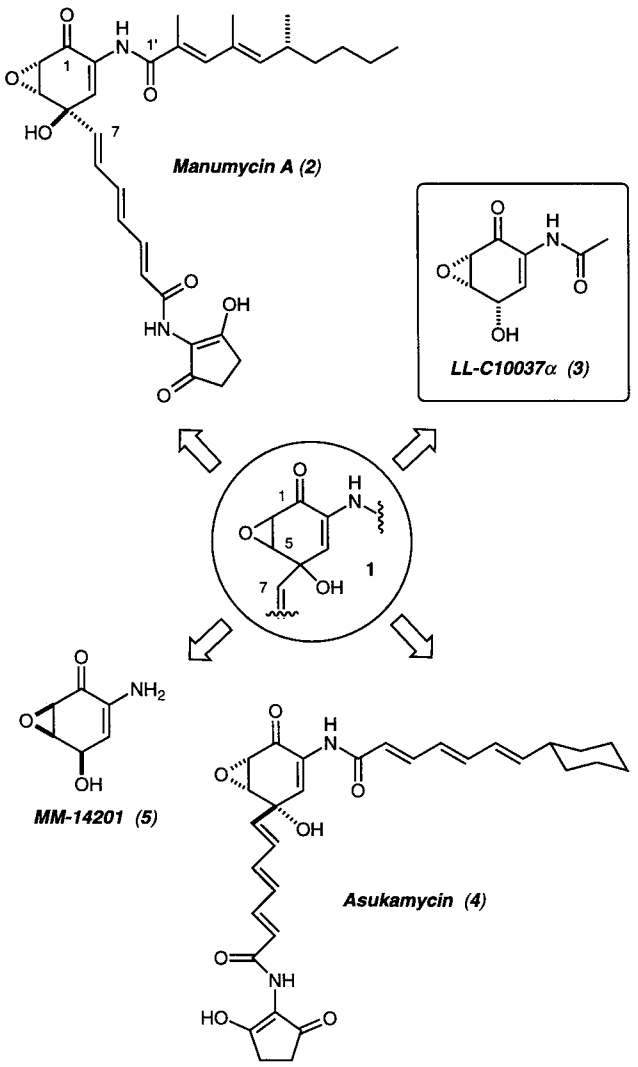
Starting with *N*-allyloxycarbonyl-protected 2,5-dimethoxyaniline, hypervalent iodine oxidation protocols and selective enone epoxidation provides the *Streptomyces* metabolite LL-C10037α in nine steps and 7–10% overall yield. In an asymmetric variant of this strategy, (*R,R*)-pentane-2,4-diol is used as a chiral acetalization agent. The resulting semiquinone spiroacetal, due to an *ortho*-acylamino substituent that restricts the 1,3-dioxane ring conformation, undergoes face-selective epoxidation and is further functionalized to give (−)-LL-C10037α in 94% ee. These pathways represent the first syntheses of the highly functionalized mC_7N core of the manumycins and have been further extended toward the preparation of analogs for SAR studies of this class of antitumor antibiotics. Manumycins inhibit the farnesylation of Ras-protein by PFTase (protein farnesyltransferase).

The *meta*-substituted aniline core (mC_7N) is a common structural feature in many natural products. It is generally observed in the aromatized or quinone form found in the antitumor antibiotics mitomycin,[2] rifamycin,[3] and maytansine.[4] Alternatively, the mC_7N-unit can also be derived from the condensation of succinyl-CoA and dihydroxyacetone, resulting in the highly oxygenated epoxyquinol unit **1** typical for the manumycin family of antibiotics.[5]

The latter group of antitumor antibiotics is represented by manumycin A **(2)**,[6] asukamycin **(4)**,[7] U-56,407,[8] U-62,162,[9] alisamycin,[10] colabomycin,[11] nisamycin,[12] and other[13] *Streptomyces* metabolites. In addition to the manumycins, a variety of smaller mC_7N antibiotics and related structures have been identified in recent years. Some representative examples include the broad-spectrum antibiotic MM-14201 **(5)**,[14] the mold metabolites chaloxone[15] and terremutin,[16] and the antimitotic compounds epoxydon,[17] bromoxone[18] and panepoxydon.[19] The *Streptomyces* metabolite LL-C10037α **(3)**[20] has antitumor activity and was shown to derive from 3-hydroxyanthranilic acid via the shikimic acid pathway.[21]

The presence of electrophilic oxiranyl ketone, nucleophilic enamide, and acid-sensitive allylic alcohol moieties on the cyclohexane ring in **1** represents a formidable challenge to synthetic strategy and methodology. Indeed, with the exception of the non-nitrogenous metabolites (±)-chaloxone[22] and bromoxone,[23] no successful synthesis within the manumycin class of mC_7N antibiotics has been reported to date. The biosynthesis of these compounds, however, as well as the isolation of manumycin analogs by feeding of aminobenzoic acids as C_7N starter units, has extensively been addressed by the groups of Floss and Zeeck.[24,25]

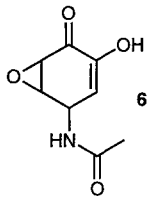
Manumycins have recently been identified as potent and selective inhibitors of Ras farnesyltransferase,[26,27] and the epoxyquinol core and its aminoacyl side chain resembling a farnesyl group were proposed as pharmacophores.[28] A significant variation[13b] of the inhibitory activity of manumycins with slightly different aminoacyl side chains toward Ras farnesyltransferase supports this theory. The fact that the Ras oncogene may contribute to as many 30% of all human cancers has triggered an intensive search for specific inhibitors of Ras p21 processing.[29,30] A synthetic route to the manumycin core would considerably facilitate structure–activity studies with Ras farnesyltransferase. In this paper, we describe the first syntheses of (+/−)- as well as (−)-LL-C10037α and an extension of this synthetic pathway for the preparation of analogs of manumycin A.[31]



Scheme 1

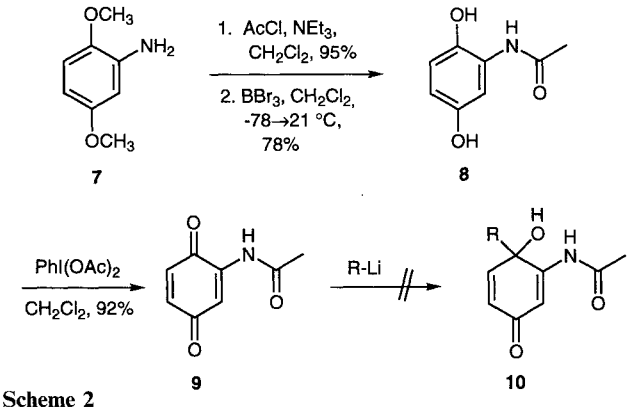
Synthesis of (+/−)-LL-C10037α

Antibiotic LL-C10037α **(3)** was first isolated in 1984 from the fermentation broth of *Streptomyces* LL-C10037 by Lee and co-workers.[20] Independently, Box et al. from Beecham Co. reported **3** as an acetylated product of MM-14201 **(5)**, produced by *Streptomyces* sp. NCIB 11813.[32] The structure of LL-C10037α was initially proposed as **6** by Lee et al.,[20] and was subsequently revised by Shen et al.[33] to **3** based upon an X-ray analysis and CD studies.



6

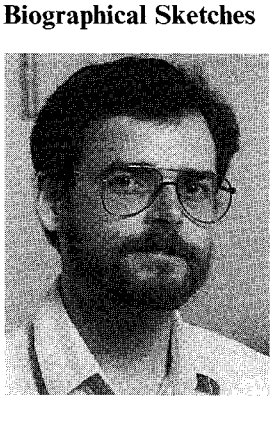
In a strategy related to our recent synthesis of the antifungal antibiotic aranorosin,[34] we selected a hypervalent iodine oxidation of an electron-rich arene for the preparation of the key synthetic intermediate of LL-C10037α (Scheme 2). Treatment of hydroquinone **8**, obtained by *N*-acetylation and demethylation of commercially readily available 2,5-dimethoxyaniline **(7)**, with iodobenzene diacetate[35] gave quinone **9** in high yield. However, subsequent addition of organolithium and -magnesium rea-



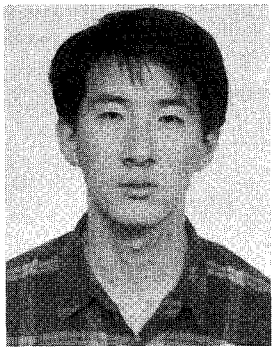
7 **8** **9** **10**

Scheme 2

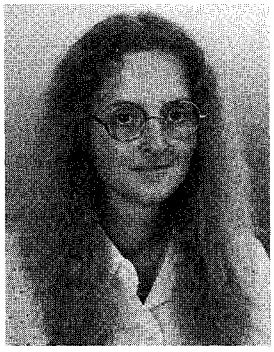
Biographical Sketches



Peter Wipf received his Diploma in 1984 and his PhD in 1987 from the University of Zürich working under the direction of Professor Heinz Heimgartner. Following a Swiss NSF postdoctoral fellowship at the University of Virginia with Professor Robert E. Ireland, he joined the faculty at the University of Pittsburgh in 1990, and was promoted to Associate Professor in 1995. His research interests are mainly in the total synthesis of natural products, organometallic and heterocyclic chemistry.

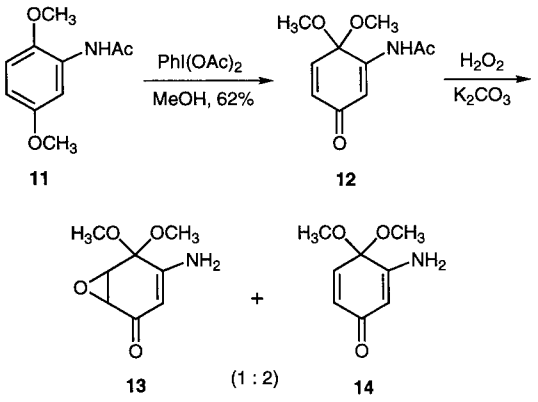


Yuntae Kim studied at Seoul National University and received B.S. and M.S. degrees in 1985 and 1987, respectively. In 1990, he joined the University of Pittsburgh and received a PhD in 1995 after having completed total syntheses of aranorosin, LL-C10037α, and stenine. He is currently a postdoctoral fellow at the California Institute of Technology.



Heike Jahn received a PhD in 1991 from the Martin-Luther University Halle-Wittenberg under the direction of Professor H.-J. Deutscher in the field of liquid crystals. After working for the Beilstein Information System, she joined the University of Pittsburgh in 1994 as a postdoctoral fellow.

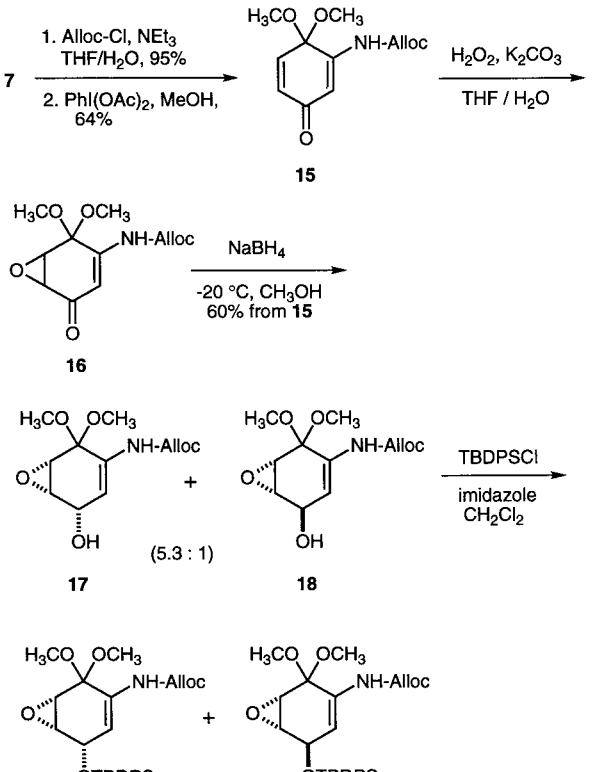
gents failed to provide the desired alcohol **10**.[36] Epoxidation of the quinone monoacetal **12** was similarly unsuccessful, resulting in extensive *N*-deacylation and poor conversion (Scheme 3). Consequently, the enamine function in **12** had to be protected with a less base-labile carbamate group.



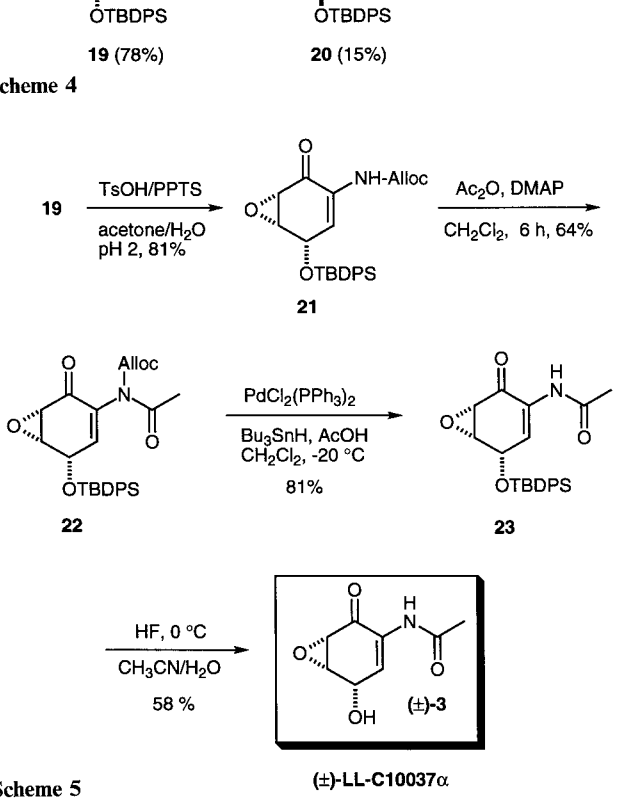
Scheme 3

N-Allyloxycarbonyl-(Alloc) protected quinone monoacetal **15** was obtained from 2,5-dimethoxyaniline (**7**) in 61% yield (Scheme 4). Similar to the corresponding *N*-acetyl substrate **12**, considerable deacylation was experienced when a mixture of **15** and H_2O_2 in aqueous THF was treated with 1.2 equivalents of K_2CO_3 in a single portion. When, however, the pH of the reaction medium was carefully maintained at 8, the epoxidation proceeded smoothly to give a partially separable mixture of the desired epoxy enone **16** and a small amount of the unreacted starting material **15**. Subsequent Luche reduction of **16** with $NaBH_4$ in the presence of $CeCl_3$ in methanol at $-20\,^{\circ}C$ afforded the *syn*- and *anti*-epoxy alcohols **17** and **18** in a 3:1 ratio. In contrast, reduction without $CeCl_3$ at $-20\,^{\circ}C$ resulted in an improved 5.3:1 mixture of **17** and **18** (60% from **15**). After silylation of the allylic alcohols with *tert*-butyldiphenylsilyl chloride (TBDPSCl), the *syn*-silyl ether **19** could be separated from the *anti*-isomer **20** by column chromatography on silica gel. With each isomer available in diastereomerically pure form, both C-4 epimers of the target structure **3** could be synthesized and compared to the natural LL-C10037α.

The major ketal **19** was deprotected in the presence of 4-toluenesulfonic acid and PPTS in aqueous acetone to give the epoxy ketone **21** in 81% yield (Scheme 5). Deprotection of the *N*-Alloc group of **21** was not considered at this stage because of the known instability of this functionality, as experienced with MM-14201.[14] Accordingly, our strategy involved direct *N*-acetylation of **21** followed by successive low-temperature *N*- and *O*-deprotection reactions with Pd(0)/Bu_3SnH[37] and HF/acetonitrile, respectively. Desilylation with tetrabutylammonium fluoride was not successful due to the base sensitivity of the product. Addition of a solution of **23** in CH_3CN to 48% aqueous HF at 0 °C, however, resulted in smooth desilylation and provided (±)-LL-C10037α in 58% yield (a 7% overall yield from **7**). The extremely broad functional group tolerance of the palladium-catalyzed *N*-deprotection reaction was crucial for the successful completion of this synthesis.

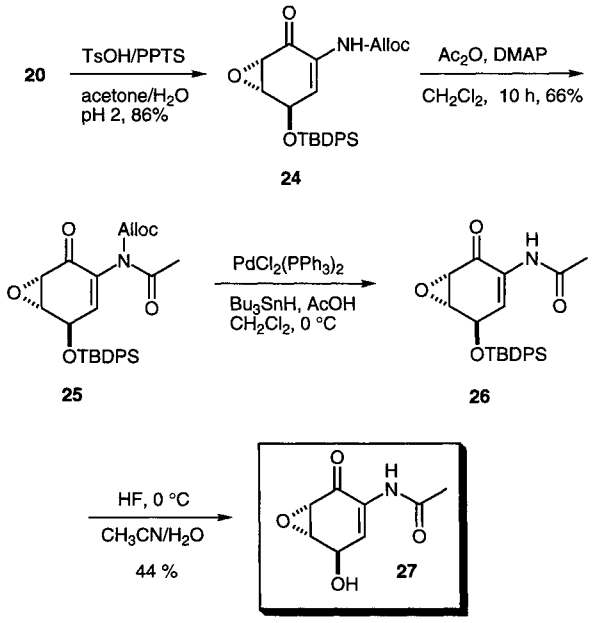


Scheme 4

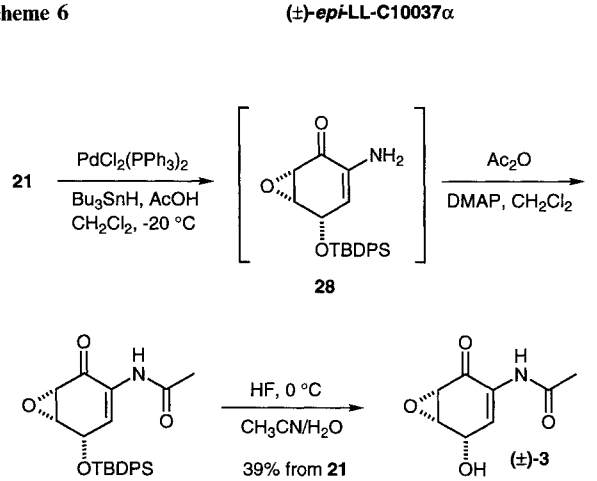


Scheme 5

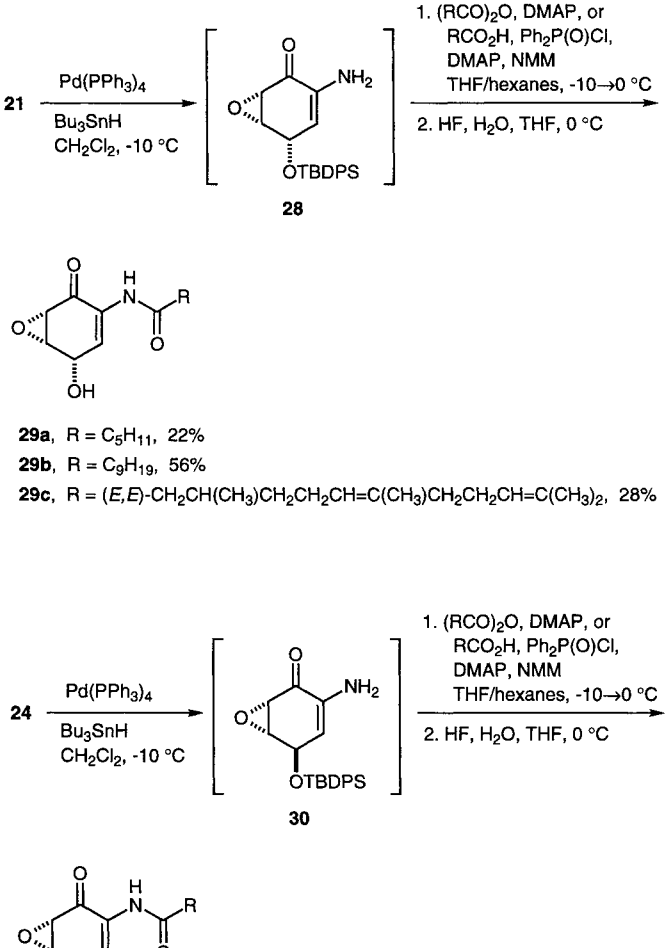
In an analogous sequence of reactions starting with the *anti*-epoxy silyl ether **20**, C-4-*epi*-(±)-LL-C10037α (**27**) was obtained in 25% yield (Scheme 6). Comparison of the ^1H and ^{13}C NMR of both synthetic epimers to those of the natural compound revealed that **3** was identical in all regards, whereas **27** was clearly different.



Scheme 6



Scheme 7



Scheme 8

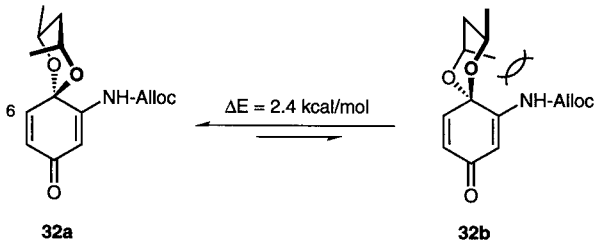
Synthesis of Analogs of LL-C10037α and Manumycin

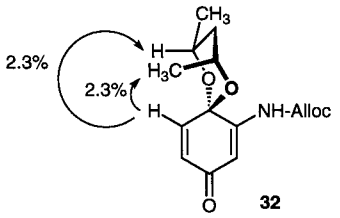
The close structural resemblance between **3** and the cyclic core (mC_7N unit) of manumycin **(2)** provided the basis for a straightforward extension of our synthetic strategy toward the preparation of analogs of the PFtase inhibitor manumycin for structure–activity studies. Specifically, we have probed the replacement of the *N*-acetyl group of LL-C10037α with aliphatic carboxylates more closely related to the polyunsaturated side chains of manumycins.

In a model study, decanoic anhydride (R = C_9H_{19}) was used as an acylating species in place of acetic anhydride. Due to the decreased reactivity of anhydrides with longer aliphatic chains, however, the second acylation on the amide nitrogen in **21** did not occur in reasonable rate. Thus, the removal of *N*-Alloc prior to the acylation was investigated in spite of the instability of the *N*-unprotected enamine **5**. Treatment of carbamate **21** with Bu_3SnH and AcOH in the presence of Pd(0) catalyst at room temperature led to a rapid consumption of starting material, presumably affording the enamine **28**, e.g. the *O*-silyl derivative of MM-14201 (Scheme 7). Without any purification, the crude intermediate was immediately reacted with acetic anhydride and DMAP in CH_2Cl_2. After desilylation of **23** with HF, (±)-LL-C10037α was obtained in 39% yield from **21**. This modified route involved fewer purification steps and provided an increased overall yield of 10% for (±)-**3**. Based upon this modified synthetic scheme, the analogs **29a, b, c** and **31a, b** were readily prepared from **21** and **24**, respectively (Scheme 8).[38] A mixed anhydride protocol with diphenylphosphinic chloride was advantageous in the acylation of enamines **28** and **30** with acids that were not directly available as their anhydrides.

Synthesis of (−)-LL-C10037α

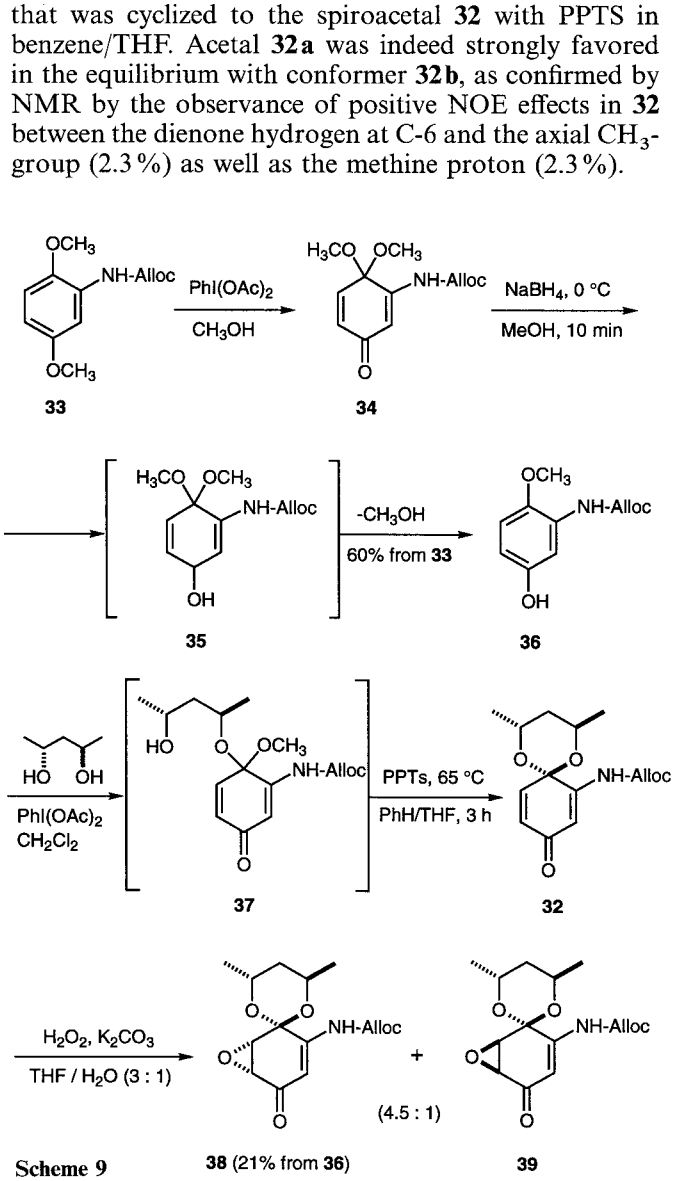
The optically active natural product was prepared by a diastereoselective epoxidation of a chiral acetal derivative of **15**. For this purpose, optically pure pentane-2,4-diol appeared to be an appropriate chiral auxiliary.[39] According to energy minimization of the chiral ketal **32**,[40] the two possible conformers **32a** and **32b** form an equilibrium in favor of **32a**.





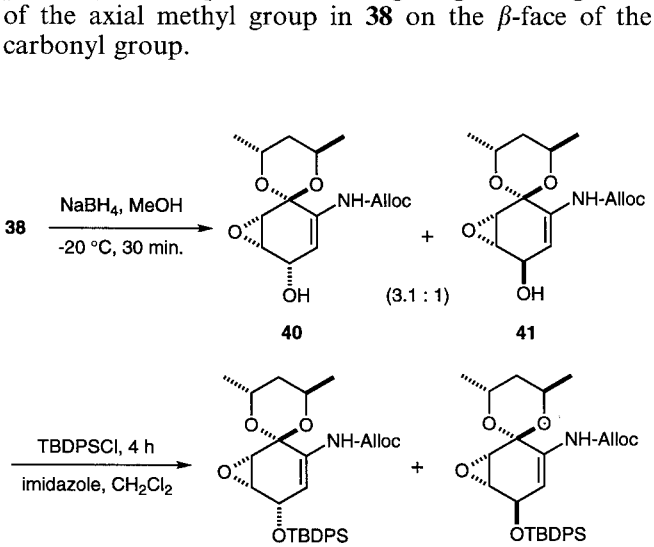
The major conformer **32a** shows different steric environments around C-6, the site of nucleophilic attack in the epoxidation reaction. The axial methyl group extending over the β-face of the planar dienone should hinder the approach of the incoming hydrogen peroxide, while either face of the minor conformer **32b** is open to the nucleophilic attack.

Since direct acetal exchange[41] between **15** and (2*R*,4*R*)-pentane-2,4-diol failed, *N*-protected dimethoxyaniline **33** was oxidized and reduced to yield the selectively deprotected phenol **36** in 60% yield (Scheme 9). Subsequent renewed hypervalent iodine oxidation in the presence of pentanediol (97% ee, Aldrich) gave a mixed acetal **37** that was cyclized to the spiroacetal **32** with PPTS in benzene/THF. Acetal **32a** was indeed strongly favored in the equilibrium with conformer **32b**, as confirmed by NMR by the observance of positive NOE effects in **32** between the dienone hydrogen at C-6 and the axial CH_3-group (2.3%) as well as the methine proton (2.3%).



Scheme 9

Addition of basic hydrogen peroxide to **32** resulted in a 4.5:1 ratio of the desired epoxy ketone **38** and its (5*S*,6*R*)-stereomer **39**. As expected for conformer **32a**, the axial methyl group restricted the access from the sterically more hindered β-face and thus promoted α-epoxidation. The major isomer **38** was reduced with $NaBH_4$ in methanol at $-20\,^{\circ}C$ to provide a 3.1:1 mixture of the two epimeric alcohols **40** and **41** (Scheme 10). Subsequent treatment of the crude alcohols with TBDPSCl and imidazole afforded the *syn*-epoxy silyl ether **42** and its *anti*-isomer **43** in 56% and 18% yield from **38**, respectively, after column chromatography on silica gel. The drop in the selectivity in the reduction of **38** compared to **16** is probably a consequence of the long-range shielding effect of the axial methyl group in **38** on the β-face of the carbonyl group.



Scheme 10

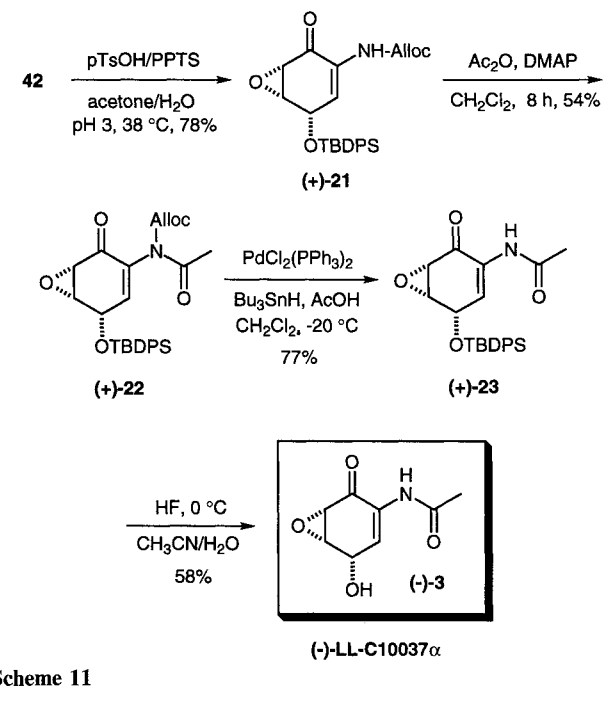
The desired major isomer **42** was deprotected with a mixture of TsOH/PPTS in acetone to give 78% of the optically active ketone **(+)-21**. The slight destabilization of the acetal **42** by the axial methyl substituent on the 1,3-dioxane ring was crucial for a successful hydrolysis step: Attempted deprotection of the all-equatorial isomer **44** under identical or milder conditions failed and led to complete decomposition of the substrate under more vigorous treatment (Scheme 12). This illustrates the sensitivity of the nucleophilic and electrophilic sites of the manumycin core structure.

Epoxyenone **(+)-21** was subsequently converted to the natural (−)-isomer of **3** in three steps analogous to the earlier transformations for racemic natural product (Scheme 11). Synthetic (−)-LL-C10037α was identical in all regards (NMR, CD) with reported data. Its optical

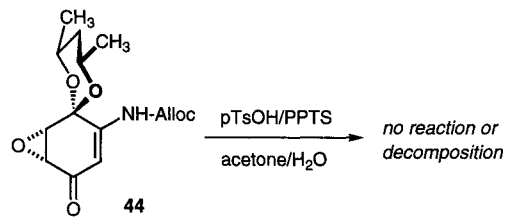
purity was determined to be 94%,[42] in close correlation with the enantiomeric excess of commercial (*R,R*)-pentane-2,4-diol, the chiral auxiliary in this synthesis.

Conclusion

Our synthetic studies toward LL-C10037α represent the first preparation of the biologically important manumycin core. Noteworthy features of this approach are the use of selective arene oxidation protocols for the preparation of quinone monoketals, a chiral acetal for achieving face-selective enone epoxidation, and a protective group strategy that successfully unmasks the challenging functional group arrays found in these natural products. Since the acyl side chains at the enamine moiety of **3** are introduced in the very last steps of the synthesis, this methodology provides a general entry toward aminoacyl epoxyquinols and SAR studies of Ras farnesyltransferase inhibitors. The synthesis of (−)-LL-C10037α establishes a basic strategy toward the enantioselective total synthesis of antibiotics of the manumycin family.



Scheme 11



Scheme 12

All glassware was dried in an oven at 150 °C prior to use. THF and dioxane were dried by distillation over Na/benzophenone under N_2. Dry CH_2Cl_2, DMF and CH_3CN were obtained by distillation from CaH_2. Other solvents or reagents were used as required expect when otherwise noted. Analytical TLC was performed on pre-coated silica gel 60 F-254 plates available from Merck. Column chromatography was performed using silica gel 60 (particle size 0.040–0.055 mm, 230–400 mesh) available from Baker. Visualization was accomplished with UV light or by staining with a basic $KMnO_4$ solution (1.5 g of $KMnO_4$, 10 g of K_2CO_3, and 2.5 mL of aq NaOH in 150 mL of distilled water) or Vaughn's reagent (4.8 g of ammonium molybdate, 0.2 g of $CeSO_4$, and 10 mL of H_2SO_4 in 90 mL of water). NMR spectra were recorded in $CDCl_3$ unless otherwise noted at either 300 MHz (^{1}H NMR), or 75 MHz (^{13}C NMR) using either a Bruker QM-300 MHz, Bruker WH-300 MHz or IBM-Bruker AF-300 MHz spectrometer at 21 °C. Chemical shifts (δ) were expressed as ppm relative to TMS. Multiplicities are expressed as follows: singlet = s, doublet = d, triplet = t, quartet = q, b = broad, AB system = AB, and multiplet = m. IR spectra were obtained on an IBM IR/32 FT IR spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Mass spectra was obtained on a VG-70-70 HF. CD spectra were obtained on a Jasco-710.

2-Acetamido-1,4-benzoquinone (9):[21b]

To a stirred solution of **8** (830 mg, 5.0 mmol) in CH_2Cl_2 (20 mL) was added at r.t. $PhI(OAc)_2$ (1.94 g, 6.0 mmol) in a single portion. After 5 min, the reaction mixture was partitioned between EtOAc (50 mL) and H_2O (50 mL). The organic layer was separated, dried (Na_2SO_4) and concentrated in vacuo. The resulting yellow solid was chromatographed on silica gel (EtOAc/hexanes, 2 : 1) to give **9** as a deep yellow solid; yield: 755 mg (92%); R_f 0.6 (EtOAc/hexanes, 2:1).

^{1}H NMR (CD_3OD): δ = 7.47 (d, 1 H, *J* = 2.4 Hz), 6.81 (d, 1 H, *J* = 10.0 Hz), 6.72 (dd, 1 H, *J* = 10.1, 2.4 Hz), 2.20 (s, 3 H).

MS (EI): *m/z* (%) = 165 (M^+, 40), 137 (10), 123 (30), 95 (25), 82 (15), 68 (20), 54 (10).

HRMS (EI) calc. for $C_8H_7NO_3$: 165.0426, found: 165.0420.

3-Acetamido-4,4-dimethoxycyclohexa-2,5-dienone (12):

A stirred solution of **11** (24.6 mg, 0.13 mmol) in MeOH (2 mL) was treated at 21 °C with $PhI(OAc)_2$ (50 mg, 0.15 mmol). After 2 h, the reaction mixture was diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The yellow solid was chromatographed on silica gel (EtOAc/hexanes, 1:1) to give **12** as a yellow solid; yield: 16 mg (62%): R_f 0.4 (EtOAc/hexanes, 2:1); mp 152 °C.

^{1}H NMR ($CDCl_3$): δ = 7.51 (bs, 1 H), 7.35 (d, 1 H, *J* = 2.0 Hz), 6.53 (d, 1 H, *J* = 10.4 Hz), 6.41 (dd, 1 H, *J* = 10.4, 2.0 Hz), 3.25 (s, 6 H), 2.19 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 186.0, 169.7, 147.0, 138.4, 133.4, 114.0, 94.3, 51.6, 25.0.

MS (EI): *m/z* (%) = 211 (M^+, 15), 196 (10), 179 (85), 164 (100), 152 (75), 140 (20), 136 (25), 128 (15), 122 (35), 110 (35), 99 (10), 95 (30), 80 (15), 68 (30), 55 (15).

HRMS (EI) calc. for $C_{10}H_{13}NO_4$: 211.0831, found: 211.0845.

Epoxidation of 12.

A solution of **12** (14 mg, 0.07 mmol) in THF (2 mL) was treated at 21 °C with 30% H_2O_2 (0.5 mL) and 0.4 N K_2CO_3 (0.1 mL). The reaction mixture was stirred for 1 h, diluted with EtOAc (10 mL), washed with brine and dried (Na_2SO_4). Chromatography of the residue on silica gel (EtOAc/hexanes, 3:1) gave an inseparable mixture of **13** and **14** as a white solid:

13: R_f 0.2 (EtOAc/hexanes, 3:1).

^{1}H NMR ($CDCl_3$): δ = 5.17 (bs, 1 H), 5.13 (d, 1 H, *J* = 2.0 Hz), 3.76 (d, 1 H, *J* = 4.1 Hz), 3.61 (s, 3 H), 3.43 (dd, 1 H, *J* = 4.1, 2.1 Hz), 3.34 (s, 3 H).

14:

^{1}H NMR ($CDCl_3$): δ = 6.40 (d, 1 H, *J* = 10.2 Hz), 6.34 (dd, 1 H, *J* = 10.2, 1.8 Hz), 5.53 (d, 1 H, *J* = 1.8 Hz), 4.94 (bs, 1 H), 3.25 (s, 6 H).

3-[(Allyloxycarbonyl)amino]-4,4-dimethoxycyclohexa-2,5-dienone (15):

2,5-Dimethoxyphenylcarbamic Acid Allyl Ester **(33)**:

A stirred solution of **7** (1 g, 6.54 mmol) in THF (10 mL) and H_2O (2 mL) was successively treated at 0 °C with Alloc-Cl (1.18 g,

9.81 mmol) followed by Et_3N (1 mL). The reaction mixture was stirred for 10 h at 21 °C, diluted with EtOAc (30 mL) and washed with a mixture of brine (20 mL) and 1 N HCl (20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting dark brown oil was chromatographed on silica gel (EtOAc/hexanes, 1:10) to give **33** as a pale yellow oil; yield: 1.62 g (95%); R_f 0.6 (EtOAc/hexanes, 1:4).

IR (neat): ν = 3426, 3000, 2944, 2836, 1734, 1605, 1536, 1482, 1231, 1051 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.80 (bs, 1 H), 7.33 (d, 1 H, J = 3.0 Hz), 6.72 (d, 1 H, J = 8.9 Hz), 6.49 (dd, 1 H, J = 8.9, 3.0 Hz), 5.95 (ddt, 1 H, J = 17.3, 10.4, 5.6 Hz), 5.35 (dq, 1 H, J = 17.3, 1.4 Hz), 5.23 (dq, 1 H, J = 10.4, 1.4 Hz), 4.65 (dt, 2 H, J = 5.6, 1.4 Hz), 3.76 (s, 3 H), 3.74 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 153.9, 152.9, 141.7, 132.4, 128.2, 118.0, 110.7, 107.2, 104.5, 65.6, 56.0, 55.5.

MS (EI): m/z (%) = 237 (M^+, 100), 222 (25), 179 (30), 164 (30), 146 (5), 136 (10), 124 (15), 109 (10), 92 (10), 79 (5), 65 (5), 57 (9), 52 (5).

HRMS (EI) calc. for $C_{12}H_{15}NO_4$: 237.1001, found: 237.0985.

3-[(Allyloxycarbonyl)amino]-4,4-dimethoxycyclohexa-2,5-dienone **(15)**:

To a stirred solution of **33** (614 mg, 2.59 mmol) in CH_3OH (10 mL) was added at 0 °C $PhI(OAc)_2$ (1.05 g, 3.11 mmol). The reaction mixture was stirred for 1 h at r.t., diluted with EtOAc, and washed with sat. aq $NaHCO_3$ (2 × 40 mL) and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a dark brown residue which was chromatographed on silica gel (EtOAc/hexanes, 1:4) to give dienone **15** as a white solid; yield: 417 mg (64%); R_f 0.25 (EtOAc/hexanes, 1:2); mp 102–103 °C.

IR (neat): ν = 3260, 1742, 1611, 1551, 1206, 1098, 1036, 963 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.07 (bs, 1 H), 7.01 (d, 1 H, J = 2.0 Hz), 6.53 (d, 1 H, J = 10.4 Hz), 6.38 (dd, 1 H, J = 10.4, 2.0 Hz), 5.92 (ddt, 1 H, J = 17.1, 10.4, 5.1 Hz), 5.33 (dt, 1 H, J = 17.1, 1.4 Hz), 5.25 (d, 1 H, J = 10.4 Hz), 4.63 (dt, 2 H, J = 5.1, 1.4 Hz), 3.23 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 185.4, 152.2, 147.9, 138.3, 133.3, 131.5, 119.1, 111.8, 94.2, 66.6, 51.5.

MS (EI): /z (%) = 253 (M^+, 8), 222 (12), 212 (4), 195 (4), 180 (30), 162 (15), 136 (25), 69 (10), 57 (10).

HRMS (EI) calc. for $C_{12}H_{15}NO_5$: 253.0950; found: 253.0936.

(2*RS*,3*RS*)-5-[(Allyloxycarbonyl)amino]-2,3-epoxy-4,4-dimethoxycyclohex-5-enone (16):

A solution of **15** (120 mg, 0.47 mmol) in THF (6 mL) was treated at 21 °C with 30% H_2O_2 (2 mL) and 0.4 N K_2CO_3 (2.4 mL). The reaction mixture was stirred for 8 h, diluted with EtOAc (20 mL), washed with brine (2 ×) and dried (Na_2SO_4). Chromatography of the concentrated residue on silica gel (EtOAc/hexanes, 1:3) gave a partially separable mixture of **15** and **16** which was used for the next step.

16: R_f 0.55 (EtOAc/hexanes, 1:1).

IR (neat): ν = 3310, 2945, 1744, 1667, 1626, 1512, 1462, 1335, 1210, 1127, 1061, 1022 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.26 (bs, 1 H), 6.77 (d, 1 H, J = 1.7 Hz), 5.92 (ddt, 1 H, J = 17.1, 10.4, 5.8 Hz), 5.34 (d, 1 H, J = 17.1 Hz), 5.27 (d, 1 H, J = 10.4 Hz), 4.63 (d, 2 H, J = 5.8 Hz), 3.81 (d, 1 H, J = 4.0 Hz), 3.62 (s, 3 H), 3.50 (dd, 1 H, J = 4.0, 1.7 Hz), 3.28 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 192.4, 151.9, 146.2, 131.5, 119.4, 106.8, 95.4, 66.8, 52.1, 51.5, 51.3, 50.6.

MS (EI): m/z (%) = 269 (M^+, 9), 238 (4), 223 (4), 210 (12), 195 (2), 180 (14), 136 (6), 108 (10), 68 (10), 57 (40).

HRMS (EI) calc. for $C_{12}H_{15}NO_6$: 269.0899, found: 269.0912.

(1*SR*,2*SR*,3*SR*)-5-[(Allyloxycarbonyl)amino]-2,3-epoxy-4,4-dimethoxycyclohex-5-enol (17) and (1*RS*,2*SR*,3*SR*)-5-[(Allyloxycarbonyl)amino]-2,3-epoxy-4,4-dimethoxycyclohex-5-enol (18):

A mixture of **15** and **16** was dissolved in CH_3OH (8 mL) and treated at 0 °C with $NaBH_4$ (36 mg, 0.94 mmol). The reaction mixture was stirred for 1.5 h at 0 °C, diluted with EtOAc (25 mL), washed with a mixture of 1 N HCl (3 mL) and brine (20 mL), separated and dried (Na_2SO_4). The filtered solution was concentrated in vacuo and chromatographed on silica gel (EtOAc/hexanes, 1:2) to give 76.4 mg (60% from **15**) of a partially separable mixture of **17** and **18** (5.3:1) that was directly used for the next step:

17: R_f 0.36 (EtOAc/hexanes, 1:1).

IR (neat): ν = 3424, 2946, 2838, 1732, 1673, 1651, 1557, 1520, 1462, 1341, 1221, 1129, 1059, 934 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.74 (bs, 1 H), 6.17 (bs, 1 H), 5.87 (ddt, 1 H, J = 17.2, 10.4, 5.7 Hz), 5.27 (dd, 1 H, J = 17.2, 1.3 Hz), 5.18 (dd, 1 H, J = 10.4, 1.3 Hz), 4.59 (dt, 1 H, J = 9.9, 2.3 Hz), 4.53 (dd, 2 H, J = 5.7, 1.3 Hz), 3.52 (m, 1 H), 3.49 (d, 1 H, J = 4.4 Hz), 3.47 (s, 3 H), 3.18 (s, 3 H), 2.85 (d, 1 H, J = 9.9 Hz).

^{13}C NMR ($CDCl_3$): δ = 153.1, 132.3, 128.2, 118.2, 111.1, 95.3, 65.7, 64.9, 53.1, 51.5, 50.9, 50.1.

MS (EI): m/z (%) = 271 (M^+, 10), 240 (10), 224 (3), 210 (35), 198 (10), 182 (10), 170 (15), 152 (25), 138 (20), 126 (80), 111 (20), 98 (20), 94 (15), 88 (20), 82 (20), 75 (20), 70 (30), 66 (15), 57 (25), 53 (20), 43 (100).

HRMS (EI) calc. for $C_{12}H_{17}NO_6$: 271.1056, found: 271.1060.

18: R_f 0.37 (EtOAc/hexanes, 1:1).

IR (neat): ν = 3422, 2946, 1734, 1684, 1520, 1458, 1345, 1221, 1125, 1061, 1017, 970, 936, 868 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.88 (bs, 1 H), 6.48 (dd, 1 H, J = 15.6, 1.2 Hz), 5.92 (ddt, 1 H, J = 17.9, 10.4, 5.6 Hz), 5.31 (dq, 1 H, J = 17.9, 1.6 Hz), 5.24 (dd, 1 H, J = 10.4, 1.3 Hz), 4.63 (dt, 1 H, J = 8.2, 1.2 Hz), 4.58 (dddd, 2 H, J = 5.7, 1.6, 1.3, 1.1), 3.53 (s, 3 H), 3.52 (m, 1 H), 3.45 (m, 1 H), 3.29 (s, 3 H), 2.12 (d, 1 H, J = 8.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 153.1, 132.2, 131.3, 118.5, 108.7, 95.8, 65.9, 63.3, 52.2, 51.2, 50.6, 49.9.

MS (EI): m/z (%) = 271 (M^+, 10), 240 (8), 224 (3), 210 (22), 198 (8), 182 (6), 166 (6), 152 (20), 138 (15), 126 (25), 111 (20), 70 (15), 57 (15).

HRMS (EI) calc. for $C_{12}H_{17}NO_6$: 271.1056, found: 271.1040.

(1*SR*,5*SR*,6*RS*)-3-[(Allyloxycarbonyl)amino]-5-(*tert*-butyldiphenylsilyloxy)-2,2-dimethoxy-7-oxabicyclo[4.1.0]hept-3-ene (19) and (1*SR*,5*RS*,6*RS*)-3-[(Allyloxycarbonyl)amino]-5-(*tert*-butyldiphenylsilyloxy)-2,2-dimethoxy-7-oxabicyclo[4.1.0]hept-3-ene (20):

A solution of a 5.3:1 mixture of **17** and **18** (520 mg, 1.92 mmol) was dissolved in CH_2Cl_2 (10 mL) and treated at 21 °C with TBDPSCl (685 mg, 2.50 mmol) and imidazole (522 mg, 7.68 mmol). The reaction mixture was stirred for 30 min, diluted with hexanes (20 mL), washed with H_2O (50 mL), separated and dried (Na_2SO_4). The filtered solution was concentrated in vacuo and chromatographed on silica gel (EtOAc/hexanes, 1:20) to give 766 mg (78%) of **19** and 147 mg (15%) of **20** as colorless oils:

19: R_f 0.50 (EtOAc/hexanes, 1:3).

IR (neat): ν = 3424, 2940, 2894, 2857, 1736, 1516, 1472, 1428, 1372, 1339, 1217, 1057, 1022, 938, 845, 824, 743, 704, 612 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.79–7.71 (m, 4 H), 7.45–7.38 (m, 6 H), 6.79 (bs, 1 H), 6.31 (bs, 1 H), 5.93 (dddd, 1 H, J = 17.3, 10.4, 5.3, 4.6 Hz), 5.33 (dd, 1 H, J = 17.3, 1.4 Hz), 5.25 (dd, 1 H, J = 10.4, 1.0 Hz), 4.71 (dd, 1 H, J = 2.2, 2.0 Hz), 4.63 (ddd, 1 H, J = 12.8, 5.3, 1.0 Hz), 4.59 (ddd, 1 H, J = 12.8, 4.6, 1.4 Hz), 3.49 (s, 3 H), 3.34 (d, 1 H, J = 4.6 Hz), 3.13 (s, 3 H), 3.11 (m, 1 H), 1.10 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 152.9, 135.9, 135.8, 133.9, 132.8, 132.4, 130.0, 129.9, 127.9, 127.8, 118.2, 111.8, 95.3, 66.8, 65.7, 52.7, 51.0, 50.8, 49.9, 26.9, 19.3.

MS (EI): m/z (%) = 452 ([M – C_4H_9]$^+$, 30), 420 (30), 394 (30), 379 (10), 362 (12), 334 (55), 319 (17), 284 (10), 258 (15), 213 (80), 199 (70), 183 (30), 167 (20), 153 (20), 135 (40), 111 (20), 84 (100).

HRMS (EI) calc. for $C_{24}H_{26}NO_6Si$ (M – C_4H_9): 452.1529, found: 452.1555.

20: R_f 0.55 (EtOAc/hexanes, 1:3).

IR (neat): ν = 3422, 2938, 2857, 1736, 1514, 1472, 1428, 1370, 1339, 1215, 1055, 1022, 936, 845, 822, 743, 704, 612 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.72–7.70 (m, 4H), 7.48–7.38 (m, 6H), 6.76 (bs, 1H), 6.38 (bs, 1H), 5.92 (ddt, 1H, J = 17.3, 10.3, 5.8 Hz), 5.32 (dd, 1H, J = 17.3, 1.4 Hz), 5.24 (dd, 1H, J = 10.3, 1.2 Hz), 4.64–4.58 (m, 3H), 3.52 (s, 3H), 3.45 (m, 1H), 3.44 (s, 3H), 3.28 (m, 1H), 1.18 (s, 9H).

^{13}C NMR ($CDCl_3$): δ = 153.2, 135.9, 135.7, 133.6, 133.0, 132.5, 130.0, 129.2, 127.9, 118.1, 109.7, 96.0, 65.7, 64.3, 53.1, 52.1, 51.0, 50.2, 26.9, 19.3.

(2*SR*,3*RS*,4*SR*)-6-[(Allyloxycarbonyl)amino]-4-(*tert*-butyldiphenylsilyloxy)-2,3-epoxycyclohex-5-enone (21):

A solution of **19** (720 mg, 1.41 mmol) in acetone (40 mL) and H_2O (5 mL) was treated at 21 °C with PPTS (326 mg, 1.30 mmol) and TsOH · H_2O (38 mg, 0.2 mmol). The reaction mixture was stirred for 4 d, diluted with hexanes (50 mL) and washed with sat. aq $NaHCO_3$, 1 N HCl (50 mL) and brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The resulting crude oil was chromatographed on silica gel (EtOAc/hexanes 1:20) to give **21** as a colorless oil; yield: 529 mg (81%); R_f 0.60 (EtOAc/hexanes, 1:3).

IR (neat): ν = 3399, 2934, 2859, 1738, 1688, 1647, 1524, 1472, 1428, 1374, 1213, 1109, 1042, 1007, 878, 857, 824, 743, 704, 610 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.83–7.76 (m, 4H), 7.50–7.41 (m, 6H), 7.08 (2 bs, 2H), 5.93 (ddt, 1H, J = 17.1, 10.4, 5.6 Hz), 5.34 (dd, 1H, J = 17.1, 1.5 Hz), 5.25 (dd, 1H, J = 10.4, 1.1 Hz), 4.85 (t, 1H, J = 2.9 Hz), 4.63 (d, 2H, J = 5.6 Hz), 3.40–3.43 (m, 1H), 3.37 (d, 1H, J = 4.0 Hz), 1.16 (s, 9H).

^{13}C NMR ($CDCl_3$): δ = 188.1, 152.8, 135.8, 135.7, 133.1, 132.3, 132.0, 130.2, 130.1, 128.0, 127.9, 123.2, 118.2, 66.1, 65.8, 53.2, 52.0, 26.8, 19.2.

MS (EI): m/z (%) = 463 (M^+, 5), 406 ([M – C_4H_9]$^+$, 40), 378 (12), 365 (15), 348 (15), 334 (15), 321 (25), 277 (35), 244 (30), 216 (25), 199 (100), 181 (20), 161 (15), 135 (35), 105 (20), 91 (25), 71 (22), 57 (18).

HRMS (EI) calc. for $C_{22}H_{20}NO_5Si$ (M – C_4H_9): 406.1111, found: 406.1073.

(2*SR*,3*RS*,4*SR*)-6-[Acetyl(allyloxycarbonyl)amino]-4-(*tert*-butyldiphenylsilyloxy)-2,3-epoxycyclohex-5-enone (22):

To a stirred solution of **21** (251 mg, 0.54 mmol) in CH_2Cl_2 (25 mL) was added at –30 °C Ac_2O (166 mg, 1.62 mmol) and DMAP (33 mg, 0.27 mmol). After stirring for 6 h at –30 °C, the reaction mixture was diluted with EtOAc (50 mL) and washed with H_2O, sat. aq $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude oily product was chromatographed on silica gel (EtOAc/hexanes, 1:6) to give **22** as a colorless oil; yield: 175 mg (64%); R_f 0.55 (EtOAc/hexanes, 1:3).

IR (neat): ν = 2936, 2859, 1754, 1703, 1428, 1370, 1258, 1186, 1111, 999, 824, 768, 743, 704, 612 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.78–7.68 (m, 4H), 7.48–7.41 (m, 6H), 6.33 (t, 1H, J = 2.7 Hz), 5.84 (dddd, 1H, J = 15.7, 10.7, 5.5, 4.9 Hz), 5.34 (dq, 1H, J = 15.7, 1.3 Hz), 5.25 (dq, 1H, J = 10.7, 1.3 Hz), 4.90 (t, 1H, J = 2.7 Hz), 4.64 (ddt, 1H, J = 13.6, 4.9, 1.3 Hz), 4.61 (ddt, 1H, J = 13.6, 5.5, 1.3 Hz), 3.46 (dt, 1H, J = 3.9, 2.7 Hz), 3.38 (d, 1H, J = 3.9 Hz), 2.56 (s, 3H), 1.12 (s, 9H).

^{13}C NMR ($CDCl_3$): δ = 188.4, 172.1, 152.5, 143.4, 135.8, 132.7, 130.9, 130.8, 130.4, 128.2, 128.1, 118.5, 67.5, 66.9, 53.8, 52.8, 26.9, 25.9, 19.3.

MS (EI): m/z (%) = 505 (M^+, 12), 489 (10), 463 ([M – CH_3CO]$^+$, 10), 447 (20), 432 (30), 421 (5), 406 (13), 390 (50), 374 (35), 348 (100), 328 (10), 312 (20), 286 (15), 270 (30), 199 (15), 181 (10), 167 (10), 155 (10), 105 (13), 91 (5), 77 (10), 71 (5), 57 (25).

HRMS (EI) calc. for $C_{28}H_{31}NO_6Si$: 505.1921, found: 505.1942.

(2*SR*,3*RS*,4*SR*)-6-Acetamido-4-(*tert*-butyldiphenylsilyloxy)-2,3-epoxycyclohex-5-enone (23):

A solution of **22** (127 mg, 0.25 mmol) in CH_2Cl_2 (20 mL) was treated at –20 °C with AcOH (45 mg, 0.75 mmol), Bu_3SnH (145 mg, 0.50 mmol) and then 0.1 M $PdCl_2(PPh_3)_2$ soln (12.5 µL, 0.5 mol% in CH_2Cl_2). The reaction mixture was stirred for 1 h at –20 °C and quenched by addition of 5% aq $NaHCO_3$ (5 mL) under vigorous stirring. The mixture was diluted with EtOAc (50 mL) and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The oily crude product was chromatographed on silica gel (EtOAc/hexanes, 1:3) to give **23** as a colorless oil; yield: 85.3 mg (81%); R_f 0.24 (EtOAc/hexanes, 1:3).

IR (neat): ν = 3360, 2932, 2857, 1680, 1516, 1472, 1428, 1372, 1237, 1113, 1076, 878, 851, 822, 783, 743, 702, 610 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.79–7.72 (m, 4H), 7.47–7.40 (m, 8H), 4.81 (t, 1H, J = 2.9 Hz), 3.41 (dt, 1H, J = 3.9, 2.9 Hz), 4.38 (d, 1H, J = 3.9 Hz), 2.10 (s, 3H), 1.12 (s, 9H).

^{13}C NMR ($CDCl_3$): δ = 188.8, 169.1, 135.9, 135.8, 133.2, 132.3, 130.3, 130.2, 128.1, 128.0, 126.0, 66.1, 53.3, 52.1, 26.9, 24.6, 19.3.

MS (EI): m/z (%) = 421 (M^+, 0.5), 406 (1), 397 (2), 378 ([M – CH_3CO]$^+$, 2), 364 ([M – C_4H_9]$^+$, 50), 336 (5), 322 (50), 304 (5), 294 (20), 278 (5), 258 (8), 244 (15), 216 (15), 199 (100), 181 (10), 156 (5), 135 (10), 115 (5), 105 (5), 96 (5), 77 (15), 57 (7).

HRMS (EI) calc. for $C_{20}H_{16}NO_4Si$ (M – C_4H_9): 364.1005, found: 364.1015.

(±)-LL-C10037α [(±)-3]:

A solution of **23** (8.7 mg, 0.02 mmol) in CH_3CN (0.5 mL) was added dropwise at 0 °C to 48% HF (3 mL). The reaction mixture was stirred for 1 h at 0 °C and poured into cold sat. aq $NaHCO_3$. The mixture was extracted with EtOAc (5 × 20 mL). The combined organic layers were washed with sat. aq $NaHCO_3$, and brine, separated, and dried (Na_2SO_4). The filtered solution was concentrated in vacuo and the solid residue was chromatographed on silica gel (EtOAc/CH_2Cl_2, 1:2) to give (±)-LL-C-10037α as a white solid; yield: 2.2 mg (58%); R_f 0.25 (EtOAc/hexanes, 2:1); mp 167 °C (dec).

IR (neat): ν = 3189, 2899, 1647, 1538, 1524, 1489, 1456, 1439, 1416, 1358, 1318, 1267, 1038, 1005, 905, 866, 785, 727, 673, 660 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.56 (bs, 1H), 7.44 (dd, 1H, J = 3.1, 2.1 Hz), 4.85 (ddd, 1H, J = 10.7, 3.2, 3.1 Hz), 3.89 (ddd, 1H, J = 3.9, 3.2, 2.1 Hz), 3.61 (d, 1H, J = 3.9 Hz), 2.27 (d, 1H, J = 10.7 Hz), 2.13 (s, 3H).

^1H NMR (DMSO-d_6): δ = 9.04 (bs, 1H), 7.05 (dd, 1H, J = 2.7, 2.3 Hz), 5.78 (d, 1H, J = 4.6 Hz), 4.78 (ddd, 1H, J = 4.6, 2.7, 2.5 Hz), 3.77 (ddd, 1H, J = 4.3, 2.5, 2.3 Hz), 3.54 (d, 1H, J = 4.3 Hz), 1.99 (s, 3H).

^{13}C NMR (DMSO-d_6): δ = 189.7, 169.5, 128.3, 63.3, 53.7, 52.2, 23.7.

MS (EI): m/z (%) = 183 (M^+, 20), 154 (15), 141 (20), 125 (15), 112 (50), 96 (10), 83 (20), 70 (25).

HRMS (EI) calc. for $C_8H_9NO_4$: 183.0536, found: 183.0504.

(±)-LL-C10037α from 21 According to Scheme 7:

A solution of **21** (13 mg, 0.03 mmol) in CH_2Cl_2 (5 mL) was treated at 0 °C with AcOH (6 mg, 0.09 mmol), Bu_3SnH (17 mg, 0.06 mmol) and then 0.1 M $PdCl_2(PPh_3)_2$ soln (3.0 µL, 0.5 mol% in CH_2Cl_2). The reaction mixture was stirred for 30 min at 21 °C and quenched by addition of 5% aq $NaHCO_3$ (5 mL) under vigorous stirring. The mixture was diluted with EtOAc (10 mL) and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude oily product **28** was immediately dissolved in CH_2Cl_2 (5 mL) and treated at 21 °C with Ac_2O (20 mg, 0.2 mmol) and DMAP (5 mg, 0.04 mmol). After 7 h, the reaction mixture was diluted with EtOAc and H_2O. The organic layer was separated, dried (Na_2SO_4) and concentrated in vacuo. The crude **23** was diluted with CH_3CN (3 mL) and reacted at 0 °C with 48% aq HF (0.5 mL). After 1 h, a cold $NaHCO_3$ solution was added slowly. The resulting mixture was partitioned between EtOAc and brine. The aqueous layer was washed with EtOAc (5 × 10 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The solid residue was chromatographed on silica gel (EtOAc/CH_2Cl_2, 1:2) to give 2.0 mg (39% from **21**) of (±)-LL-C10037α as a white solid. The ^1H NMR of the product was identical to that of (±)-LL-C10037α obtained from the procedure indicated in Scheme 5.

(2*SR*,3*RS*,4*RS*)-6-[(Allyloxycarbonyl)amino]-4-(*tert*-butyldiphenylsilyloxy)-2,3-epoxycyclohex-5-enone (24):

A solution of **20** (116 mg, 0.23 mmol) in acetone (10 mL) and H_2O (1.3 mL) was treated at 21 °C with PPTS (62 mg, 0.26 mmol) and TsOH · H_2O (8 mg, 0.04 mmol). The reaction mixture was stirred for 4 d, diluted with hexanes (20 mL) and washed with sat. aq $NaHCO_3$, 1 N HCl (10 mL) and brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude oil was chromatographed on silica gel (EtOAc/hexanes, 1:20) to give **24** as a colorless oil; yield: 91 mg (86%); R_f 0.71 (EtOAc/hexanes, 1:3).

IR (neat): ν = 3399, 2934, 2859, 1738, 1688, 1647, 1524, 1472, 1428, 1374, 1312, 1213, 1159, 1109, 1042, 1005, 914, 878, 857, 824, 789, 767, 743, 704, 610 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.76–7.69 (m, 4H), 7.49–7.36 (m, 6H), 7.17 (s, 1H), 7.05 (bs, 1H), 5.92 (ddt, 1H, J = 17.1, 10.4, 5.7 Hz), 5.34 (dd, 1H, J = 17.1, 1.5 Hz), 5.26 (dd, 1H, J = 10.4, 1.3 Hz), 4.88 (dd, 1H, J = 5.4, 1.0 Hz), 4.61 (ddd, 2H, J = 5.7, 1.3, 1.0 Hz), 3.68 (m, 1H), 3.52 (dd, 1H, J = 3.3, 0.9 Hz), 1.12 (s, 9H).

^{13}C NMR ($CDCl_3$): δ = 188.4, 152.8, 135.8, 135.3, 134.8, 133.1, 132.8, 132.1, 130.2, 129.9, 129.6, 128.0, 127.7, 121.1, 118.4, 65.9, 64.6, 57.8, 52.3, 26.9, 19.3.

MS (EI): m/z (%) = 463 (M^+, 1), 406 ([M – C_4H_9]$^+$, 30), 378 (15), 365 (20), 348 (20), 334 (20), 321 (25), 277 (30), 256 (10), 244 (20), 199 (100), 181 (20), 161 (10), 135 (30), 115 (15), 105 (20), 91 (25), 77 (25), 57 (35).

HRMS (EI) calc. for $C_{22}H_{20}NO_5Si$ (M – C_4H_9): 406.1111, found: 406.1094.

(2*SR*,3*RS*,4*RS*)-6-[Acetyl(allyloxycarbonyl)amino]-4-(*tert*-butyldiphenylsilyloxy)-2,3-epoxycyclohex-5-enone (25):

To a stirred solution of **24** (80 mg, 0.17 mmol) in CH_2Cl_2 (10 mL) were added at – 10 °C Ac_2O (33 mg, 0.32 mmol) and DMAP (7 mg, 0.05 mmol). After 10 h stirring at – 10 °C, the reaction mixture was diluted with EtOAc (10 mL) and washed with water, and sat. aq $NaHCO_3$ and brine. The organic layer was separated, dried (Na_2SO_4) and concentrated in vacuo. The crude oily product was chromatographed on silica gel (EtOAc/hexanes, 1:6) to give **25** as a colorless oil; yield: 58 mg (66%). R_f 0.51 (EtOAc/hexanes, 1:3).

IR (neat): ν = 2934, 1752, 1717, 1700, 1258, 1186, 1111, 704 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.73–7.67 (m, 4H), 7.51–7.38 (m, 6H), 6.17 (dd, 1H, J = 4.9, 2.3 Hz), 5.81 (ddt, 1H, J = 17.3, 11.1, 5.4 Hz), 5.27 (dd, 1H, J = 17.3, 1.4 Hz), 5.21 (dd, 1H, J = 11.1, 1.4 Hz), 4.81 (dt, 1H, J = 4.9, 0.9 Hz), 4.59 (dt, 1H, J = 5.4, 1.4 Hz), 3.73 (ddd, 1H, J = 4.9, 3.0, 0.9 Hz), 3.57 (dd, 1H, J = 3.0, 0.9 Hz), 2.57 (s, 3H), 1.10 (s, 9H).

^{13}C NMR ($CDCl_3$): δ = 188.4, 171.8, 152.6, 140.9, 135.8, 133.1, 132.6, 132.3, 130.9, 130.5, 130.4, 128.2, 128.1, 118.8, 67.6, 64.8, 58.0, 53.8, 26.9, 25.9, 19.3.

MS (EI): m/z (%) = 505 (M^+, 6), 489 (10), 463 ([M – CH_3CO]$^+$, 8), 447 (20), 432 (30), 406 (20), 390 (60), 374 (50), 348 (100), 328 (8), 312 (20), 286 (8), 270 (20), 250 (10), 224 (20), 199 (12), 181 (10), 135 (18), 105 (10), 91 (2), 77 (20).

HRMS (EI) calc. for $C_{28}H_{31}NO_6Si$: 505.1921, found: 505.1893.

(2*SR*,3*RS*,4*RS*)-6-Acetamido-4-(*tert*-butyldiphenylsilyloxy)-2,3-epoxycyclohex-5-enone (26):

A solution of **25** (52 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) was treated at 0 °C with AcOH (23 mg, 0.38 mmol), Bu_3SnH (73 mg, 0.25 mmol) and then 0.1 M $PdCl_2(PPh_3)_2$ soln (6.3 µL, 0.5 mol% in CH_2Cl_2). The reaction mixture was stirred for 30 min at 0 °C and quenched by addition of 5% aq $NaHCO_3$ (5 mL) under vigorous stirring. The mixture was diluted with EtOAc (20 mL) and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude oily product was chromatographed on silica gel (EtOAc/hexanes, 1:6) to give 45 mg of **26** still contaminated with organotin side products; R_f 0.23 (EtOAc/hexanes, 1:3).

IR (neat): ν = 3362, 2932, 2859, 1680, 1653, 1516, 1472, 1428, 1374, 1111, 1076, 880, 851, 824, 785, 743, 704 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.73–7.67 (m, 4H), 7.60 (bs, 1H), 7.47–7.39 (m, 7H), 4.84 (dt, 1H, J = 6.5, 1.1 Hz), 3.67 (dq, 1H, J = 3.4, 1.1 Hz), 3.51 (dd, 1H, J = 3.4, 1.1 Hz), 2.09 (s, 3H), 1.09 (s, 9H).

^{13}C NMR ($CDCl_3$): δ = 189.0, 169.0, 135.9, 135.8, 133.1, 132.7, 130.3, 129.8, 128.0, 123.6, 64.6, 57.8, 52.3, 27.0, 24.7, 19.3.

MS (EI): m/z (%) = 421 (M^+, 0.2), 405 (0.2), 397 (1), 378 ([M – CH_3CO]$^+$, 0.2), 378 (1.2), 364 ([M – C_4H_9]$^+$, 50), 336 (5), 322 (25), 304 (5), 294 (20), 278 (5), 258 (8), 244 (15), 216 (20), 199 (100), 181 (15), 156 (10), 135 (15), 115 (10), 105 (10), 77 (25), 57 (10).

HRMS (EI) calc. for $C_{20}H_{16}NO_4Si$ (M – C_4H_9): 364.1005, found: 364.0994.

(±)-*epi*-LL-C10037α (27):

A solution of crude **26** in CH_3CN (1 mL) was added dropwise at 0 °C to 48% aq HF (3 mL). The reaction mixture was stirred for 2 h at 0 °C, poured into cold sat. aq $NaHCO_3$, and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ and brine, and dried (Na_2SO_4). The filtered solution was concentrated in vacuo and the solid residue was chromatographed on silica gel (EtOAc/CH_2Cl_2, 1:2) to give **27** as a white solid; yield: 8.3 mg (44% from **25**); R_f 0.25 (EtOAc/hexanes, 1:1); mp 154 °C (dec).

^1H NMR ($CDCl_3$): δ = 7.69 (bs, 1H), 7.60 (dd, 1H, J = 5.3, 2.4 Hz), 4.89 (dddd, 1H, J = 7.4, 6.8, 5.3, 1.1 Hz), 3.85 (dddd, 1H, J = 6.8, 3.7, 2.4, 1.1 Hz), 3.61 (dd, 1H, J = 3.7, 1.1 Hz), 2.64 (dd, 1H, J = 7.4, 1.1 Hz), 2.14 (s, 3H).

^1H NMR (DMSO-d_6): δ = 9.08 (bs, 1H), 7.27 (dd, 1H, J = 5.4, 2.3 Hz), 5.73 (dd, 1H, J = 5.5, 1.2 Hz), 4.63 (dddd, 1H, J = 6.0, 5.5, 5.4, 0.9 Hz), 3.76 (dddd, 1H, J = 6.0, 3.8, 2.3, 1.2 Hz), 3.64 (dd, 1H, J = 3.8, 0.9 Hz), 2.01 (s, 3H).

^{13}C NMR (DMSO-d_6): δ = 189.6, 169.7, 130.4, 125.6, 61.8, 57.4, 52.7, 23.8.

MS (EI): m/z (%) = 183 (M^+, 25), 170 (100), 149 (25), 141 (20), 125 (20), 112 (50), 97 (15), 83 (35), 71 (15), 56 (15).

General Procedure A for the Preparation of *O*-TBDPS Ethers of Epoxyquinols 29a, b and 31a:

A solution of epoxide **21** or **24** (51.0 mg, 0.11 mmol) in anhydr. CH_2Cl_2 (1 mL) was treated at – 10 °C with 5 mol% of $Pd(PPh_3)_4$ and Bu_3SnH (48 mg, 0.165 mmol). After stirring for 1 h at this temperature, the reaction mixture was quickly partitioned between cold (0 °C) CH_2Cl_2/aq $NaHCO_3$ (1:1). The organic layer was washed with cold brine and dried for 15 min ($MgSO_4$). Most of the CH_2Cl_2 was evaporated under reduced pressure at r.t. After addition of cold hexanes, the remaining CH_2Cl_2 was removed in vacuo. To the resulting hexanes solution of enamine **28** or **30** were added DMAP (26.9 mg, 0.22 mmol) and anhydride (0.33 mmol), and the mixture was stirred at 0 °C until the starting material disappeared (TLC, hexanes/EtOAc, 3:1). The solvent was evaporated and the crude product chromatographed on silica gel (hexanes/EtOAc, 20:1) and on Florisil (hexanes/EtOAc, 10:1) to give the *O*-TBDPS ether of **29a, b** or **31a** as a yellow oil.

(2SR,3RS,4SR)-4-(tert-Butyldiphenylsilyloxy)-2,3-epoxy-6-(hexanoylamino)cyclohex-5-enone:

According to the general procedure A, **21** (92.6 mg, 0.20 mmol) gave 40 mg (41%) of the *O*-TBDPS ether of **29a** that was used directly for the next reaction; R_f 0.6 (EtOAc/hexanes, 1:3).

(2SR,3RS,4SR)-4-(tert-Butyldiphenylsilyloxy)-6-(decanoylamino)-2,3-epoxycyclohex-5-enone:

According to the general procedure A, **21** (102.0 mg, 0.22 mmol) gave 72.6 mg (62%) of the *O*-TBDPS ether of **29b**; R_f 0.6 (EtOAc/hexanes, 1:3).

IR (neat): ν = 3362, 2921, 1671, 1508, 1456, 1418, 1356, 1186, 1103, 1071, 905, 872, 847, 815, 777, 733, 700, 606 cm^{-1}.

^1H NMR: δ = 7.78–7.70 (m, 4H), 7.49 (dd, 1H, J = 4.0, 1.7 Hz), 7.45–7.38 (m, 7H), 4.80 (dd, 1H, J = 4.0 Hz), 3.36–3.34 (m, 2H), 2.26 (t, 2H, J = 7.5 Hz), 1.65–1.55 (m, 2H), 1.35–1.15 (m, 12H), 1.10 (s, 9H), 0.86 (t, 3H, J = 7.0 Hz).

^{13}C NMR: δ = 188.8, 172.2, 135.9, 135.8, 133.2, 132.2, 130.2, 130.1, 128.0, 127.9, 125.8, 66.1, 53.2, 52.0, 37.7, 31.8, 29.4, 29.2, 29.1, 26.8, 25.3, 22.6, 19.2, 14.1.

MS (EI): *m/z* (%): 533 (M^+, 2), 476 (4), 432 (30), 322 (91), 294 (55), 254 (45), 244 (39), 199 (100), 104 (46), 91 (36), 77 (63), 57 (69).

HRMS (EI) calc for $C_{32}H_{43}NO_4Si$: 533.2961, found: 533.3005.

(2SR,3RS,4RS)-4-(tert-Butyldiphenylsilyloxy)-6-(decanoylamino)-2,3-epoxycyclohex-5-enone:

According to the general procedure A, **24** (51.0 mg, 0.11 mmol) gave 14.7 mg (25%) of the *O*-TBDPS ether of **31a**: R_f 0.7 (EtOAc/hexanes, 1:3).

IR (neat): ν = 3355, 2905, 2840, 1705, 1665, 1644, 1624, 1501, 1464, 1454, 1416, 1354, 1100, 1059, 816, 733, 696 cm^{-1}.

^1H NMR: δ = 7.70–7.64 (m, 4H), 7.56 (bs, 1H), 7.44–7.36 (m, 7H), 4.82 (d, 1H, J = 5.3 Hz), 3.62 (bs, 1H), 3.48 (dd, 1H, J = 3.0, 0.8 Hz), 2.26 (t, 2H, J = 7.0 Hz), 1.65–1.55 (m, 2H), 1.30–1.20 (m, 12H), 1.06 (s, 9H), 0.86 (t, 3H, J = 6.6 Hz).

^{13}C NMR: δ = 189.0, 172.2, 135.9, 135.8, 133.2, 132.7, 130.3, 129.8, 128.0, 127.8, 123.4, 64.7, 57.8, 52.3, 37.9, 31.9, 29.8, 29.5, 29.4, 29.3, 29.2, 27.0, 25.4, 22.7, 19.3, 14.2.

MS (EI): *m/z* (%) = 534 ($[M+H]^+$, 5), 476 ($[M-C_4H_9]^+$, 100), 442 (7), 352 (6), 322 (6), 199 (79), 165 (30), 125 (6), 91 (27), 71 (6), 57 (7).

HRMS (EI) calc. for $C_{28}H_{34}NO_4Si$ $[M-C_4H_9]$: 476.2257, found: 476.2265.

General Procedure B for the Preparation of *O*-TBDPS Ethers of Epoxyquinols 29c and 31b:

To a stirred solution of 2,3-dihydrofarnesic acid (78.7 mg, 0.33 mmol) and $Ph_2P(O)Cl$ (85.9 mg, 0.363 mmol) in THF/hexanes (3 mL, 2:1) was added dropwise at −10 °C NMM (33.4 mg, 0.33 mmol) under N_2. Stirring was continued for 3 h, and DMAP (26.9 mg, 0.22 mmol) was added followed by dropwise addition of a solution of the crude amine **28** or **30** prepared according to general procedure A in hexanes. The reaction mixture was warmed to 0 °C and stirred until the reaction was complete (TLC, hexanes/EtOAc, 3:1). After addition of Et_2O and H_2O, the organic layer was washed with sat. aq $NaHCO_3$ (3 ×), brine (1 ×), and dried ($MgSO_4$). Chromatography on silica gel (hexanes/EtOAc, 20:1) and on Florisil (hexanes/EtOAc, 20:1) gave the *O*-TBDPS ethers of **29c** and **31b**.

(2SR,3RS,4SR)-4-(tert-Butyldiphenylsilyloxy)-2,3-epoxy-6-(3,7,11-trimethyldodeca-6,10-dienoylamino)cyclohex-5-enone:

According to the general procedure B, **21** (51.0 mg, 0.11 mmol) gave 41.1 mg (62%) of the *O*-TBDPS ether of **29c**; R_f 0.7 (EtOAc/hexanes, 1:3).

IR (neat): ν = 3353, 2915, 1672, 1505, 1462, 1449, 1420, 1360, 1102, 1069 cm^{-1}.

^1H NMR: δ = 7.78–7.71 (m, 4H), 7.51 (bs, 1H), 7.45–7.37 (m, 7H), 5.15–5.05 (m, 2H), 4.81 (dd, 1H, J = 2.7, 2.5 Hz), 3.36 (s, 2H), 2.45–2.35 (m, 1H), 2.10–1.90 (m, 8H), 1.66 (s, 3H), 1.58 (s, 6H), 1.40–1.10 (m, 2H), 1.10 (s, 9H), 0.94 (d, 3H, J = 6.3 Hz).

^{13}C NMR: δ = 188.9, 171.7, 136.0, 135.9, 135.3, 134.9, 133.3, 132.3, 131.4, 130.3, 130.2, 129.7, 128.1, 128.0, 127.8, 125.9, 124.4, 124.1, 66.2, 53.3, 52.2, 45.5, 39.8, 36.8, 30.5, 26.9, 26.8, 26.6, 25.8, 25.4, 19.6, 19.3, 17.8, 16.1.

MS (EI): *m/z* (%) = 599 (M^+, 3), 542 (24), 498 (6), 434 (6), 380 (12), 322 (52), 199 (100), 109 (40), 69 (70).

HRMS (EI) calc. for $C_{37}H_{49}NO_4Si$: 599.3431, found: 599.3512.

(2SR,3RS,4RS)-4-(tert-Butyldiphenylsilyloxy)-2,3-epoxy-6-(3,7,11-trimethyldodeca-6,10-dienoylamino)cyclohex-5-enone:

According to the general procedure B, **24** (51.0 mg, 0.11 mmol) gave 37.2 mg (56%) of the *O*-TBDPS ether of **31b**; R_f 0.8 (EtOAc/hexanes, 1:3).

IR (neat): ν = 3380, 2922, 1663, 1503, 1453, 1416, 1366, 1102, 1063, 816 cm^{-1}.

^1H NMR: δ = 7.72–7.65 (m, 4H), 7.57 (bs, 1H), 7.47–7.33 (m, 7H), 5.15–5.05 (m, 2H), 4.82 (d, 1H, J = 5.3 Hz), 3.64 (dd, 1H, J = 3.4, 2.2 Hz), 3.49 (d, 1H, J = 3.4 Hz), 2.4–2.35 (m, 2H), 2.20–1.90 (m, 8H), 1.67 (s, 3H), 1.59 (s, 6H), 1.40–1.10 (m, 2H), 1.07 (s, 9H), 0.97 (d, 3H, J = 6.6 Hz).

^{13}C NMR: δ = 189.0, 171.6, 135.8, 135.7, 134.8, 132.5, 130.2, 129.6, 127.9, 127.7, 124.3, 124.0, 123.4, 64.5, 57.7, 52.2, 45.4, 39.7, 36.7, 30.4, 26.8, 26.6, 26.5, 25.7, 25.3, 19.4, 19.2, 19.0, 17.7, 15.9.

General Procedure C for the Formation of 29a, b, c and 31a, b by *O*-Desilylation:

A solution of the *O*-TBDPS ether of **29** or **31** (0.03 mmol) in THF (1 mL) was treated at 0 °C with 48% aq HF (3 mL). After stirring at 0 °C for 3 h, the reaction mixture was quenched by addition of sat. aq $NaHCO_3$, diluted with EtOAc, washed with brine and dried ($MgSO_4$). Purification by chromatography on Florisil (hexanes/EtOAc, 2:1) gave alcohols **29a, b, c** and **31 a, b**.

(2SR,3SR,4SR)-2,3-Epoxy-6-(hexanoylamino)-4-hydroxycyclohex-5-enone **(29a)**:

According to the general procedure C, the *O*-TBDPS ether of **29a** (40 mg, 0.08 mmol) gave 10.8 mg (22% from **21**) of **29a**; R_f 0.2 (EtOAc/hexanes, 1:2); mp 138 °C.

IR (neat): ν = 3318, 2907, 1686, 1676, 1628, 1566, 1547, 1531, 1512, 1042, 870 cm^{-1}.

^1H NMR: δ = 7.54 (bs, 1H), 7.44 (dd, 1H, J = 3.0, 2.7 Hz), 4.83 (dt, 1H, J = 10.0, 6.2, 3.0 Hz), 3.86 (dd, 1H, J = 6.2, 3.6 Hz), 3.57 (d, 1H, J = 3.6 Hz), 2.70 (d, 1H, J = 10.0 Hz), 2.29 (t, 2H, J = 7.6 Hz), 1.68–1.58 (m, 2H), 1.35–1.20 (m, 6H), 0.87 (t, 3H, J = 6.8 Hz).

^{13}C NMR: δ = 188.6, 172.6, 128.3, 124.8, 64.5, 54.0, 52.6, 37.6, 31.3, 25.0, 22.3, 13.9.

MS (EI): *m/z* (%) = 239 (M^+, 18), 210 (15), 183 (16), 141 (39), 125 (57), 112 (81), 99 (73), 71 (100).

HRMS (EI) calc. for $C_{12}H_{17}NO_4$: 239.1158, found: 239.1151.

(2SR,3SR,4SR)-6-(Decanoylamino)-2,3-epoxy-4-hydroxycyclohex-5-enone **(29b)**:

According to the general procedure C, the *O*-TBDPS ether of **29b** (54.2 mg, 0.10 mmol) gave 27.6 mg (91%) of **29b**; R_f 0.2 (EtOAc/hexanes, 1:2); mp 124–125 °C.

IR (neat): ν = 3308, 2896, 2460, 1672, 1630, 1543, 1044, 870 cm^{-1}.

^1H NMR: δ = 7.55 (bs, 1H), 7.44 (dd, 1H, J = 3.0, 2.7 Hz), 4.82 (dt, 1H, J = 10.8, 6.2, 3.0 Hz), 3.86 (dd, 1H, J = 6.2, 3.6 Hz), 3.58 (d, 1H, J = 3.6 Hz), 2.28 (t, 2H, J = 7.5 Hz), 2.13 (d, 1H, J = 10.8 Hz), 1.65–1.55 (m, 2H), 1.35–1.20 (m, 12H), 0.85 (t, 3H, J = 6.7 Hz).

^{13}C NMR: δ = 188.6, 172.6, 128.2, 125.0, 64.4, 54.0, 52.5, 37.7, 31.8, 29.4, 29.2, 29.1, 25.3, 22.6, 14.1.

MS (EI): *m/z* (%): 295 (M^+, 26), 266 (27), 183 (48), 141 (76), 125 (37), 112 (100), 85 (33), 71 (58), 57 (53).

HRMS (EI) calc. for $C_{16}H_{25}NO_4$: 295.1784, found 295.1793.

(2SR,3SR,4SR)-2,3-Epoxy-4-hydroxy-6-(3,7,11-trimethyldodeca-6,10-dienoylamino)cyclohex-5-enone **(29c)**:

According to the general procedure C, the *O*-TBDPS ether of **29c** (41 mg, 0.11 mmol) gave 11.1 mg (28% from **21**) of **29c**; R_f 0.25 (EtOAc/hexanes, 1:2); mp 67 °C.

IR (neat): ν = 3335, 2911, 1640, 1530, 1449, 1368, 1264, 1046, 870 cm^{-1}.

^1H NMR: δ = 7.51 (bs, 1H), 7.45 (dd, 1H, J = 2.7, 2.6 Hz), 5.15–5.05 (m, 2H), 4.83 (bd, 1H, J = 9.7 Hz), 3.86 (dd, 1H, J = 6.2, 3.1 Hz), 3.58 (d, 1H, J = 3.9 Hz), 2.50–2.40 (bd, 1H, J = 9.7 Hz), 2.32 (dd, 1H, J = 13.6, 5.1 Hz), 2.10–1.96 (m, 8H), 1.65 (s, 3H), 1.57 (s, 6H), 1.50–1.15 (m, 2H), 0.93 (d, 3H, J = 6.3 Hz).

^{13}C NMR: δ = 188.6, 172.0, 131.4, 128.5, 124.6, 124.0, 64.6, 54.2, 52.8, 42.8, 39.8, 37.0, 30.5, 26.8, 25.8, 25.4, 19.8, 17.8, 16.2.

MS (EI): *m/z* (%) = 361 (M^+, 3), 345 (3), 327 (5), 258 (13), 177 (13), 143 (62), 125 (85), 109 (72), 81 (34), 69 (100).

HRMS (EI): calc for $C_{21}H_{31}NO_4$: 361.2253, found: 361.2268.

(2SR,3SR,4RS)-6-(Decanoylamino)-2,3-epoxy-4-hydroxycyclohex-5-enone **(31a)**:

According to the general procedure C, the *O*-TBDPS ether of **31a**

(14.7 mg, 0.03 mmol) gave 6.0 mg (73%) of **31a**; R_f 0.35 (EtOAc/hexanes, 1:2); mp 82°C.

IR (neat): ν = 3337, 2913, 1692, 1661, 1644, 1630, 1547, 1526, 1514 cm^{-1}.

^1H NMR: δ = 7.67 (bs, 1H), 7.61 (dd, 1H, J = 5.4, 2.4 Hz), 4.88 (ddd, 1H, J = 6.7, 5.4, 1.1 Hz), 3.83 (dddd, 1H, J = 5.9, 3.6, 2.4, 1.1 Hz), 3.60 (dd, 1H, J = 3.6, 1.1 Hz), 2.62 (d, 1H, J = 6.7 Hz), 2.23 (t, 2H, J = 7.6 Hz), 1.70–1.60 (m, 2H), 1.35–1.20 (m, 12H), 0.85 (t, 3H, J = 6.6 Hz).

^{13}C NMR: δ = 188.9, 172.9, 130.1, 123.1, 63.1, 57.3, 52.2, 37.8, 31.8, 29.4, 29.2, 29.1, 25.3, 22.6, 14.1.

MS (EI): m/z (%) = 295 (M^+, 24), 279 (10), 266 (24), 183 (22), 141 (64), 125 (82), 112 (89), 85 (45), 71 (80), 57 (100).

HRMS (EI) calc. for $C_{16}H_{25}NO_4$: 295.1784, found: 295.1772.

(2SR,3SR,4RS)-2,3-Epoxy-4-hydroxy-6-(3,7,11-trimethyldodeca-6,10-dienoylamino)cyclohex-5-enone **(31b)**:

According to the general procedure C, the *O*-TBDPS ether of **31b** (37 mg, 0.06 mmol) gave 10.2 mg (25% from **24**) of **31b**; R_f 0.4 (EtOAc/hexanes, 1:2); mp 77°C.

IR (neat): ν = 3343, 2909, 1659, 1507, 1443, 1368, 1213, 1107, 1024, 868 cm^{-1}.

^1H NMR: δ = 7.65 (bs, 1H), 7.65–7.58 (dd, 1H, J = 5.2, 2.4 Hz), 5.12–5.05 (m, 2H), 4.87 (bd, 1H, J = 5.2 Hz), 3.82 (dd, 1H, J = 2.2, 2.0 Hz), 3.59 (dd, 1H, J = 3.1, 0.8 Hz), 2.32 (ddd, 1H, J = 14.0, 5.7, 1.5 Hz), 2.11–1.93 (m, 8H), 1.65 (s, 3H), 1.57 (s, 6H), 1.40–1.15 (m, 2H), 0.93 (d, 3H, J = 6.4 Hz).

^{13}C NMR: δ = 188.8, 172.4, 135.4, 131.4, 130.2, 124.4, 123.9, 123.1, 63.2, 57.4, 52.3, 45.5, 39.8, 36.8, 30.5, 29.8, 26.8, 25.8, 25.4, 19.6, 17.8, 16.1.

MS (EI): m/z (%) = 361 (M^+, 9), 345 (6), 327 (6), 258 (9), 219 (11), 143 (70), 125 (89), 109 (90), 69 (100).

HRMS (EI) calc. for $C_{21}H_{31}NO_4$: 361.2253, found: 361.2290.

3-[(Allyloxycarbonyl)amino]-4-methoxyphenol (36):

To a solution of **33** (876 mg, 3.70 mmol) in abs. CH_3OH (15 mL) was added at 0°C $PhI(OAc)_2$ (1.43 g, 4.44 mmol). The reaction mixture was stirred for 1 h at r.t. and diluted with EtOAc. The organic layer was washed with sat. aq $NaHCO_3$ (2 × 50 mL) and brine, separated, and dried ($MgSO_4$). Filtration and evaporation gave a dark brown residue which was filtered through a short plug of silica gel (hexane/EtOAc, 3:1) to remove iodobenzene. After the removal of the solvents, the crude product **34** was diluted with CH_3OH (20 mL) and treated at 0°C with $NaBH_4$ (169 mg, 4.44 mmol). After 10 min, the reaction mixture was quenched with acetone (2 mL) and diluted with EtOAc (50 mL). The organic layer was washed with 1 N HCl and brine, separated and dried (Na_2SO_4). Column chromatography on silica gel (EtOAc/hexanes, 1:3) of the crude product gave **36** as a white solid; yield: 495 mg (60%); R_f 0.65 (EtOAc/hexanes, 1:1); mp 103–104°C.

IR (neat): ν = 3337, 2942, 1694, 1615, 1541, 1489, 1466, 1437, 1385, 1213, 1057, 1028, 995, 967, 934, 864, 764, 731, 619 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.89 (bs, 1H), 7.46 (bs, 2H), 6.72 (d, 1H, J = 8.8 Hz), 6.54 (dd, 1H, J = 8.8, 3.0 Hz), 5.97 (ddt, 1H, J = 17.2, 10.4, 5.7 Hz), 5.39 (dd, 1H, J = 17.2, 1.3 Hz), 5.27 (dd, 1H, J = 10.4, 0.9 Hz), 4.69 (d, 2H, J = 5.7 Hz), 3.77 (s, 3H).

^{13}C NMR ($CDCl_3$): δ = 153.7, 150.6, 141.3, 131.9, 127.5, 118.5, 111.3, 108.9, 105.9, 66.2, 56.1.

MS (EI): m/z (%) = 223 (M^+, 16), 165 (10), 150 (20), 138 (6), 122 (5), 110 (12), 69 (1), 55 (20), 44 (100).

HRMS (EI) calc. for $C_{11}H_{13}NO_4$: 223.0845, found: 223.0852.

(2*R*,4*R*)-7-[(Allyloxycarbonyl)amino]-2,4-dimethyl-1,5-dioxaspiro-[5.5]nona-7,10-dien-9-one (32):

To a solution of **36** (40.1 mg, 0.18 mmol) in dry CH_2Cl_2 (5 mL) was added at 21°C $PhI(OAc)_2$ (65 mg, 0.2 mmol) and (−)-pentane-2,4-diol (94 mg, 0.90 mmol). After 15 min, the reaction mixture was diluted with EtOAc (10 mL) and the organic layer was washed with sat. aq $NaHCO_3$, separated and dried (Na_2SO_4). The filtered solution was concentrated in vacuo and passed through a short plug of silica gel to give crude **37**. A solution of **37** in benzene (5 mL) and THF (5 mL) was treated with PPTS (23 mg, 0.09 mmol) and heated to 65°C for 4 h. The reaction was cooled to r.t. and diluted with EtOAc (30 mL). The organic layer was washed with H_2O and brine, separated and dried (Na_2SO_4). The oily product was chromatographed on silica gel (EtOAc/hexanes, 1:3) to give **32** as a colorless oil; yield: 23.2 mg (44%); R_f 0.5 (EtOAc/hexanes, 1:1); $[\alpha]_D$ +18.4° (c = 0.9, CH_3OH, 22°C).

IR (neat): ν = 3303, 2979, 2936, 1732, 1667, 1653, 1634, 1615, 1507, 1456, 1385, 1343, 1314, 1208, 1130, 1109, 1009, 934, 882, 772 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.02 (d, 1H, J = 10.5 Hz), 6.93 (bs, 1H), 6.83 (d, 1H, J = 1.9 Hz), 6.11 (dd, 1H, J = 10.5, 1.9 Hz), 5.97 (ddt, 1H, J = 18.5, 10.4, 5.9 Hz), 5.37 (d, 1H, J = 18.5 Hz), 5.30 (d, 1H, J = 10.4 Hz), 4.67 (dd, 2H, J = 6.0, 1.0 Hz), 4.41 (ddq, 1H, J = 7.6, 6.2, 5.8 Hz), 4.38 (ddq, 1H, J = 6.6, 5.8, 5.2 Hz), 1.86 (ddd, 1H, J = 14.0, 7.6, 5.2 Hz), 1.78 (dt, 1H, J = 14.0, 5.8 Hz), 1.38 (d, 3H, J = 6.6 Hz), 1.32 (d, 3H, J = 6.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 185.7, 152.2, 150.0, 139.0, 131.9, 127.9, 119.3, 109.2, 90.6, 67.1, 66.8, 64.0, 37.1, 22.6, 22.2.

MS (EI): m/z (%) = 293 (M^+, 16), 252 (2), 234 (1), 208 (9), 166 (15), 151 (15), 140 (15), 122 (25), 91 (30), 82 (10), 69 (50), 55 (15).

HRMS (EI) calc. for $C_{15}H_{19}NO_5$: 293.1263, found: 293.1274.

(2*R*,4*R*,7*S*,8*R*)-11-[(Allyloxycarbonyl)amino]-7,8-epoxy-2,4-dimethyl-1,5-dioxaspiro[5.5]non-10-en-9-one (38):

A solution of **32** (52 mg, 0.18 mmol) in THF (5 mL) was treated at 20°C with 30% H_2O_2 (1 mL, 8.83 mmol) and K_2CO_3 (3 mg, 0.02 mmol). The reaction mixture was stirred for 6 h at 21°C and diluted with EtOAc (20 mL). The organic layer was washed with brine (2 × 30 mL), separated and dried (Na_2SO_4). A ^1H NMR analysis of the crude oil showed a 4.5:1 ratio of isomers **38** and **39** with 60% conversion. The crude product was chromatographed on silica gel (EtOAc/hexanes, 1:3) to give **38** as a colorless oil; yield: 27 mg (49%); R_f 0.6 (EtOAc/hexanes, 1:1); $[\alpha]_D$ +204.6° (c = 1.6, CH_3OH, 22°C).

IR (neat): ν = 3320, 2979, 1746, 1684, 1653, 1647, 1507, 1458, 1206, 1148, 1113, 1019 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.30 (bs, 1H), 6.63 (d, 1H, J = 2.0 Hz), 5.93 (ddt, 1H, J = 17.2, 10.3, 6.0 Hz), 5.35 (dq, 1H, J = 17.2, 1.3 Hz), 5.28 (dq, 1H, J = 10.3, 1.3 Hz), 4.66 (ddt, 1H, J = 13.0, 6.0, 1.3 Hz), 4.62 (ddt, 1H, J = 13.0, 6.0, 1.3 Hz), 4.46 (ddq, 1H, J = 7.0, 6.3, 6.2 Hz), 4.11 (ddq, 1H, J = 7.7, 6.2, 5.7 Hz), 3.87 (d, 1H, J = 4.1 Hz), 3.48 (dd, 1H, J = 4.1, 2.0 Hz), 1.86–1.81 (m, 2H), 1.40 (d, 3H, J = 6.2 Hz), 1.23 (d, 3H, J = 6.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 192.8, 151.9, 148.1, 131.6, 119.5, 105.4, 94.5, 66.9, 65.7, 65.4, 52.5, 52.3, 39.7, 21.9, 21.8.

MS (EI): m/z (%) = 309 (M^+, 14), 282 (2), 268 (2), 240 (3), 224 (4), 212 (1), 196 (6), 182 (7), 138 (20), 110 (15), 82 (10), 69 (100), 55 (20).

HRMS (EI) calc. for $C_{15}H_{19}NO_6$: 309.1212, found: 309.1191.

(2*R*,4*R*,7*S*,8*S*,9*S*)-11-[(Allyloxycarbonyl)amino]-7,8-epoxy-2,4-dimethyl-1,5-dioxaspiro[5.5]non-10-en-9-ol (40) and (2*R*,4*R*,7*S*,8*S*,9*R*)-11-[(Allyloxycarbonyl)amino]-7,8-epoxy-2,4-dimethyl-1,5-dioxaspiro[5.5]non-10-en-9-ol (41):

A solution of **38** (25 mg, 0.08 mmol) in CH_3OH (2 mL) was treated at −20°C with $NaBH_4$ (6 mg, 0.16 mmol) and stirred for 30 min at the same temperature. The reaction mixture was quenched with acetone (1 mL) and diluted with EtOAc (30 mL). The organic layer was washed with brine, separated, and dried (Na_2SO_4). The crude product was chromatographed on silica gel (EtOAc/hexanes, 1:2) to give 25 mg (quant.) of a 3.1:1 mixture of **40** and **41** as a white solid. **40**: R_f 0.4 (EtOAc/hexanes, 1:1).

IR (neat): ν = 3347, 2977, 2940, 1727, 1516, 1381, 1335, 1217, 1156, 1115, 1007 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.77 (s, 1H), 6.04 (bs, 1H), 5.92–5.87 (m, 1H), 5.30 (d, 1H, J = 16.8 Hz), 5.22 (d, 1H, J = 10.4 Hz), 4.65–4.53 (m, 4H), 4.33 (m, 1H), 4.08 (m, 1H), 3.58–3.44 (m, 3H), 2.35 (d, 1H, J = 10.3 Hz), 1.77–1.71 (m, 2H), 1.32 (d, 3H, J = 6.2 Hz), 1.18 (d, 3H, J = 6.1 Hz).

^{13}C NMR ($CDCl_3$): δ = 153.1, 132.4, 130.5, 118.3, 109.6, 94.2, 65.8, 65.3, 65.0, 64.5, 53.4, 52.6, 39.8, 21.9, 21.8.

MS (EI): *m/z* (%) = 311 (M^+, 4), 294 (1), 282 (2), 270 (1), 253 (1), 227 (3), 208 (1.5), 196 (4), 184 (5), 168 (3), 156 (8), 140 (8), 124 (5), 112 (8), 69 (30), 55 (20), 45 (20).

HRMS (EI) calc. for $C_{15}H_{21}NO_6$: 311.1395, found: 311.1395.

41: ^{1}H NMR ($CDCl_3$): δ = 6.93 (s, 1 H), 6.37 (d, 1 H, J = 4.1 Hz), 5.92–5.87 (m, 1 H), 5.30 (d, 1 H, J = 16.8 Hz), 5.22 (d, 1 H, J = 10.4 Hz), 4.65–4.53 (m, 4 H), 4.33 (m, 1 H), 4.08 (m, 1 H), 3.58–3.44 (m, 3 H), 2.17 (d, 1 H, J = 10.2 Hz), 1.32 (d, 3 H, J = 6.1 Hz), 1.18 (d, 3 H, J = 6.1 Hz).

^{13}C NMR ($CDCl_3$): δ = 152.9, 133.5, 132.3, 118.5, 107.4, 94.6, 65.5, 64.3, 63.5, 52.0, 51.2, 39.8, 21.9, 21.8.

(2*R*,4*R*,7*S*,8*R*,9*S*)-11-[(Allyloxycarbonyl)amino]-9-(*tert*-butyldiphenylsilyloxy)-7,8-epoxy-2,4-dimethyl-1,5-dioxaspiro[5.5]non-10-ene (42) and (2*R*,4*R*,7*S*,8*R*,9*R*)-11-[(Allyloxycarbonyl)amino]-9-(*tert*-butyldiphenylsilyloxy)-7,8-epoxy-2,4-dimethyl-1,5-dioxaspiro[5.5]non-11-ene (43):

A 3.1:1 mixture of **40** and **41** (25 mg, 0.08 mmol) was dissolved in CH_2Cl_2 (3 mL) and treated at 21 °C with TBDPSCl (33 mg, 0.12 mmol) and imidazole (27 mg, 0.4 mmol). The reaction mixture was stirred for 4 h, diluted with hexanes (10 mL), washed with H_2O (10 mL), separated and dried (Na_2SO_4). The filtered solution was concentrated in vacuo and chromatographed on silica gel (EtOAc/hexanes, 1:20) to give 25 mg (56 %) of **42** and 8 mg (18 %) of **43** as colorless oils.

42: R_f 0.3 (EtOAc/hexanes, 1:6); $[\alpha]_D$ +91.8° (c = 3.2, CH_2Cl_2, 21 °C).

IR (neat): ν = 3370, 2932, 2857, 1736, 1509, 1213, 1154, 1109, 1080, 1044, 1015, 704 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.78–7.70 (m, 4 H), 7.45–7.38 (m, 6 H), 6.79 (bs, 1 H), 6.0–5.9 (m, 1 H), 5.34 (dq, 1 H, J = 17.3, 1.5 Hz), 5.26 (d, 1 H, J = 10.4, 1.2 Hz), 4.75 (t, 1 H, J = 2.2 Hz), 4.65–4.60 (m, 2 H), 4.30 (dq, 1 H, J = 13.3, 6.6 Hz), 4.07 (ddq, 1 H, J = 7.8, 6.4, 6.4 Hz), 3.39 (d, 1 H, J = 4.5 Hz), 3.15 (dt, 1 H, J = 4.5, 2.2 Hz), 1.73–1.68 (m, 2 H), 1.32 (d, 3 H, J = 6.6 Hz), 1.13 (d, 3 H, J = 6.4 Hz), 1.09 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 153.2, 136.0, 135.9, 134.0, 133.0, 132.6, 129.9, 129.8, 127.9, 127.7, 118.2, 110.9, 94.4, 66.7, 65.8, 65.2, 64.5, 53.1, 52.1, 40.1, 29.7, 26.9, 21.9, 21.8, 19.3.

MS (FAB, MNBA/NaCl): *m/z* (%) 572 ([M + Na]$^+$, 8), 566 (1), 550 (7), 532 (1), 520 (1), 512 (2), 492 (22), 472 (6), 448 (4), 424(4), 406 (14), 391 (6), 378 (4), 365 (8), 345 (6), 321 (4), 294 (90), 277 (10), 244 (10), 208 (70), 176 (20), 154 (40), 135 (95), 121 (25), 105 (20), 91 (30), 69 (100).

43: R_f 0.35 (EtOAc/hexanes, 1:6); $[\alpha]_D$ −9.5° (c = 1.1, CH_2Cl_2, 21 °C).

IR (neat): ν = 3414, 2930, 1738, 1732, 1532, 1505, 1470, 1456, 1428, 1377, 1333, 1213, 1154, 1109, 1061, 1026, 702, 612 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.76–7.69 (m, 4 H), 7.43–7.26 (m, 6 H), 6.87 (s, 1 H), 6.16 (bs, 1 H), 6.0–5.9 (m, 1 H), 5.31 (dd, 1 H, J = 17.2, 1.3 Hz), 5.24 (dd, 1 H, J = 10.4, 1.3 Hz), 4.63–4.56 (m, 3 H), 4.37 (dq, 1 H, J = 13.3, 6.6 Hz), 4.22 (ddq, 1 H, J = 6.7, 6.7, 6.7 Hz), 3.54 (d, 1 H, J = 3.7 Hz), 3.27 (d, 1 H, J = 3.7, 1.3 Hz), 1.79 (t, 2 H, J = 7.2 Hz), 1.34 (d, 3 H, J = 6.6 Hz), 1.31 (d, 3 H, J = 6.7 Hz), 1.07 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 152.9, 136.0, 135.8, 134.1, 133.5, 132.6, 132.4, 129.8, 127.7, 118.3, 107.8, 94.7, 65.8, 65.3, 64.6, 64.2, 53.0, 52.1, 40.1, 29.8, 27.0, 22.2, 21.9, 19.4.

MS (EI): *m/z* (%) 520 (8), 492 ([M − C_4H_9]$^+$, 15), 434 (7), 406 (33), 392 (8), 348 (12), 294 (10), 244 (20), 208 (100), 135 (35), 106 (12), 69 (70).

HRMS (EI) calc. for $C_{27}H_{30}NO_6Si$ (M − C_4H_9): 492.1843, found: 492.1843.

(2*S*,3*R*,4*S*)-6-[(Allyloxycarbonyl)amino]-4-(*tert*-butyldiphenylsilyloxy)-2,3-epoxycyclohex-5-enone [(+)-21]:

A solution of **42** (34 mg, 0.06 mmol) in acetone (5 mL) and H_2O (1 mL) was treated at 21 °C with PPTS (14 mg, 0.06 mmol) and TsOH · H_2O (1.7 mg). The reaction mixture was stirred for 2 d at 38 °C, diluted with hexanes (20 mL) and washed with sat. aq $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4) and concentrated in vacuo. The crude oil was chromatographed on silica gel (EtOAc/hexanes, 1:20) to give ketone **(+)-21** as a colorless oil; yield: 22 mg (78 %); $[\alpha]_D$ +9.5° (c = 1.6, CH_3OH, 22 °C).

^{1}H NMR ($CDCl_3$): δ = 7.81–7.73 (m, 4 H), 7.48–7.40 (m, 6 H), 7.07 (bs, 1 H), 7.03 (s, 1 H), 5.93 (ddt, 1 H, J = 17.1, 10.4, 5.6 Hz), 5.34 (dd, 1 H, J = 17.1, 1.3 Hz), 5.25 (dd, 1 H, J = 10.4, 1.3 Hz), 4.82 (t, 1 H, J = 2.9 Hz), 4.62 (d, 2 H, J = 5.6 Hz), 3.39 (m, 2 H), 1.13 (s, 9 H).

The racemic mixture of this ketone was fully characterized as **21**.

(2*S*,3*R*,4*S*)-6-[Acetyl(allyloxycarbonyl)amino[-4-(*tert*-butyldiphenylsilyloxy)-2,3-epoxycyclohex-5-enone [(+)-22]:

To a solution of **(+)-21** (20 mg, 0.04 mmol) in CH_2Cl_2 (3 mL) were added at −20 °C Ac_2O (8 mg, 0.08 mmol) and DMAP (1.8 mg). After 8 h stirring at −20 °C, the reaction mixture was diluted with EtOAc (10 mL) and washed successively with H_2O, sat. aq $NaHCO_3$, 0.1 N HCl and brine. The organic layer was separated, dried (Na_2SO_4) and concentrated in vacuo. The crude oily product was chromatographed on silica gel (EtOAc/hexanes, 1:6) to give **(+)-22** as a colorless oil; yield: 12 mg (54 %); $[\alpha]_D$ +2.32° (c = 1.3, CH_3OH, 21 °C).

^{1}H NMR ($CDCl_3$): δ = 7.78–7.67 (m, 4 H), 7.49–7.42 (m, 6 H), 6.34 (t, 1 H, J = 2.7 Hz), 5.84 (dddd, 1 H, J = 15.7, 10.7, 5.5, 4.9 Hz), 5.34 (dq, 1 H, J = 15.7, 1.3 Hz), 5.25 (dq, 1 H, J = 10.7, 1.3 Hz), 4.89 (t, 1 H, J = 2.7 Hz), 4.64 (ddt, 1 H, J = 13.6, 4.9, 1.3 Hz), 4.61 (ddt, 1 H, J = 13.6, 5.5, 1.3 Hz), 3.46 (dt, 1 H, J = 3.9, 2.7 Hz), 3.38 (d, 1 H, J = 3.9 Hz), 2.56 (s, 3 H), 1.11 (s, H).

The racemic mixture of this ketone was fully characterized as **22**.

(2*S*,3*R*,4*S*)-6-Acetamido-4-(*tert*-butyldiphenylsilyloxy)-2,3-epoxycyclohex-5-enone [(+)-23]:

A solution of **(+)-22** (12 mg, 0.02 mmol) in CH_2Cl_2 (3 mL) was treated at −20 °C with AcOH (4.3 µL, 0.07 mmol), Bu_3SnH (14 mg, 0.05 mmol) and then 0.1 M $PdCl_2(PPh_3)_2$ soln (1.2 µL, 0.5 mol% in CH_2Cl_2). The reaction mixture was stirred for 1 h at −20 °C and quenched by addition of 5 % aq $NaHCO_3$ (5 mL) under vigorous stirring. The mixture was diluted with EtOAc (15 mL) and brine. The organic layer was separated, dried (Na_2SO_4) and concentrated under reduced pressure. The crude oily product was chromatographed on silica gel (EtOAc/hexanes, 1:3) to give **(+)-23** as a colorless oil; yield: 8 mg (77 %); $[\alpha]_D$ +34.5° (c = 1.1, CH_3OH, 21 °C).

^{1}H NMR ($CDCl_3$): δ = 7.79–7.72 (m, 4 H), 7.47–7.40 (m, 8 H), 4.81 (t, 1 H, J = 2.9 Hz), 3.41 (dt, 1 H, J = 3.9, 2.9 Hz), 4.38 (d, 1 H, J = 3.9 Hz), 2.10 (s, 3 H), 1.13 (s, 9 H).

The racemic mixture of this ketone was fully characterized as **23**.

(−)-LL-C10037α [(−)-3]:

A solution of **(+)-23** (7 mg, 0.018 mmol) in CH_3CN (0.5 mL) was added dropwise at 0 °C to 40 % aq HF (2 mL). The reaction mixture was stirred for 1 h at 0 °C and poured into cold sat. aq $NaHCO_3$. The mixture was extracted with EtOAc (5 × 20 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ and brine, separated, and dried (Na_2SO_4). The filtered solution was concentrated in vacuo and the solid residue was chromatographed on silica gel (EtOAc/CH_2Cl_2, 1:2) to give **(−)-3**; yield: 1.8 mg (58 %); $[\alpha]_D$ −190.6° (c = 0.08, CH_3OH, 21 °C).

^{1}H NMR ($CDCl_3$): δ = 7.56 (bs, 1 H), 7.44 (dd, 1 H, J = 3.1, 2.1 Hz), 4.85 (ddd, 1 H, J = 10.6, 3.2, 3.1 Hz), 3.88 (ddd, 1 H, J = 3.9, 3.2, 2.1 Hz), 3.60 (d, 1 H, J = 3.9 Hz), 2.33 (d, 1 H, J = 10.6 Hz), 2.13 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 188.6, 169.3, 128.5, 124.7, 64.6, 54.2, 52.7, 24.7.

The racemic mixture of this compound was fully characterized as **3**.

J. Scheler and W. Vuksan have contributed to the synthesis of analogs of LL-C10037α. We would like to thank them for their work and the NMR (Dr. F.-T. Lin) and Mass Spec (Dr. K. Somayajula) labs at

the University of Pittsburgh for assisting us in the spectral characterization. Support of this project by the National Science Foundation is also gratefully acknowledged.

(1) Eli Lilly Grantee, 1993–1995; Alfred P. Sloan Research Fellow, 1994–1996; NSF Presidential Faculty Fellow, 1994–1999; Camille Dreyfus Teacher-Scholar, 1995–1997.
(2) Lefemine, D.V.; Dann, M., Barbatschi, F.; Hausmann, W.K.; Zbinovsky, V.; Monnikendam, P.; Adam, J., Bohonos, N. *J. Am. Chem. Soc.* **1962**, *84*, 3184.
(3) Prelog, V. *Pure Appl. Chem.* **1963**, *7*, 551.
(4) Kupchan, S.M.; Komoda, Y.; Court, W.A.; Thomas, G.J.; Smith, R.M.; Karim, A.; Gilmore, C.J.; Haltiwanger, R.C.; Bryan, R.F. *J. Am. Chem. Soc.* **1972**, *94*, 1354.
(5) Thiericke, R.; Zeeck, A.; Nakagawa, A.; Omura, S.; Herrold, R.E.; Wu, S.T.S.; Beale, J.M.; Floss, H.G. *J. Am. Chem. Soc.* **1990**, *112*, 3979.
(6) Buzzetti, F.; Gäumann, E.; Hütter, R.; Keller-Schierlein, W.; Neipp, L.; Prelog, V.; Zähner, H. *Pharm. Acta Helv.* **1963**, *38*, 871.
(7) Cho, H.; Sattler, I.; Beale, J.M.; Zeeck, A.; Floss, H.G. *J. Org. Chem.* **1993**, *58*, 7925.
(8) Brodasky, T.F.; Stroman, D.W.; Dietz, A.; Mizsak, S. *J. Antibiot.* **1983**, *36*, 950.
(9) Slechta, L.; Cialdella, J.I.; Mizsak, S.A.; Hoeksema, H. *J. Antibiot.* **1982**, *35*, 556.
(10) Chatterjee, S.; Vijayakumar, E.; Franco, C.; Blumbach, J.; Ganguli, B.N. *J. Antibiot.* **1993**, *46*, 1027.
(11) Grote, R.; Zeeck, A.; Drautz, H.; Zähner, H. *J. Antibiot.* **1988**, *41*, 1178.
(12) (a) Hayashi, K.; Nakagawa, M.; Fujita, T.; Tanimori, S.; Nakayama, M. *J. Antibiot.* **1993**, *46*, 1904.
(b) Hayashi, K.; Nakagawa, M.; Fujita, T.; Tanimori, S.; Nakayama, M. *J. Antibiot.* **1994**, *47*, 1110.
(13) (a) UCF1-A and UCF1-B: Hara, M.; Akasaka, K.; Akinaga, S.; Okabe, M.; Nakano, H.; Gomez, R.; Wood, D.; Uh, M.; Tamanoi, F. *Proc. Nat. Acad. Sci. USA* **1993**, *90*, 2281.
(b) Manumycins B-E: Sattler, I.; Gröne, C.; Zeeck, A. *J. Org. Chem.* **1993**, *58*, 6583.
Shu, Y.Z.; Huang, S.; Wang, R.R.; Lam, K.S.; Klohr, S.E.; Volk, K.J.; Pirnik, D.M.; Wells, J.S.; Fernandes, P.B.; Patel, P.S. *J. Antibiot.* **1994**, *47*, 324.
(14) Box, S.J.; Gilpin, M.L.; Gwynn, M.; Hanscomb, G.; Spear, S.R.; Brown, A.G. *J. Antibiot.* **1983**, *36*, 1631.
(15) Fex, T.; Wickberg, B. *Acta Chem. Scand.* **1981**, *B 35*, 97.
(16) Miller, M.W. *Tetrahedron* **1968**, *24*, 4839.
(17) Closs, A.; Mauli, R.; Sigg, H.P. *Helv. Chim. Acta* **1966**, *49*, 204.
(18) Higa, T.; Okuda, R.K.; Severns, R.M.; Scheuer, P.J.; He, C.-H.; Changfu, X.; Clardy, J. *Tetrahedron* **1987**, *43*, 1063.
(19) Kis, Z.; Closse, A.; Sigg, H.P.; Hruban, L.; Snatzke, G. *Helv. Chim. Acta* **1970**, *53*, 1577.
(20) Lee, M.D.; Fantini, A.A.; Morton, G.O.; James, J.C.; Borders, D.B.; Testa, R.T. *J. Antibiot.* **1984**, *37*, 1149.
(21) (a) Whittle, Y.G.; Gould, S.J. *J. Am. Chem. Soc.* **1987**, *109*, 5043.
(b) Gould, S.J.; Shen, B.; Whittle, Y.G. *J. Am. Chem. Soc.* **1989**, *111*, 7932.
(22) Fex, T. *Tetrahedron Lett.* **1981**, *22*, 2707.
(23) Gautier, E.C.L.; Lewis, N.J.; McKillop, A.; Taylor, R.J.K. *Tetrahedron Lett.* **1994**, *35*, 8759.
(24) For leading references, see. Floss, H.G.; Casati, R.; Cho, H.; Beale, J.M. *Pure Appl. Chem.* **1989**, *61*, 485.
(25) Thiericke, R.; Zeeck, A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2123.
(26) Hara, M.; Han, M. *Proc. Nat. Acad. Sci. USA* **1995**, *92*, 3333.
(27) Nagase, T.; Kawata, S.; Yamazaki, E.; Ishiguro, H.; Matuzawa, Y. *Hepatology* **1993**, *18*, 190.
(28) Tamanoi, F.; Sun, C.R.; Mitsuzawa, H. 207th National Meeting of the American Chemical Society: San Diego, CA, March 13–17, 1994; MEDI 280.
(29) Boguski, M.S.; McCormick, F. *Nature (London)* **1993**, *366*, 643.
(30) (a) Travis, J. *Science* **1993**, *260*, 1877.
(b) Tamanoi, F. *TIBS* **1993**, *18*, 349 and refs. cited therein.
(31) For a preliminary communication of our synthesis of (+/−)-LL-C10037α, see: Wipf, P.; Kim, Y. *J. Org. Chem.* **1994**, *59*, 3518.
(32) Box, S.J.; Gilpin, M.L.; Gwynn, M.; Hanscomb, G.; Spear, S.R.; Brown, A.G. *J. Antibiot.* **1983**, *36*, 1631.
(33) Shen, B.; Whittle, Y.G.; Gould, S.J.; Keszler, D.A. *J. Org. Chem.* **1990**, *55*, 4422.
(34) (a) Wipf, P.; Kim, Y. *J. Org. Chem.* **1993**, *58*, 4774.
(b) Wipf, P.; Kim, Y.; Fritch, P.C. *J. Org. Chem.* **1993**, *58*, 7195.
(35) (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927.
(b) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677.
(36) Quinone **9** was extremely sensitive to basic media and decomposed rapidly even in 5% $NaHCO_3$ soln.
(37) Dangles, O.; Guibe, F.; Balavoine, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, *52*, 4984.
(38) The specific activities of these analogs in PFtase inhibition will be reported separately.
(39) For reviews on the use of chiral acetals in directing cyclopropanation reactions and other applications in asymmetric synthesis, see:
(a) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477.
(b) Sakai, K.; Suemune, H. *Tetrahedron: Asymmetry* **1993**, *4*, 2109.
For the use of a chiral acetal in a diastereoselective enone epoxidation, see:
(c) Corey, E.J.; Wu, L.I. *J. Am. Chem. Soc.* **1993**, *115*, 9327.
(40) The MM2* force field in Macromodel was used: MacroModel V3.5X; Mohamadi, F.; Richards, N.G.J.; Guida, W.C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W.C. *J. Comput. Chem.* **1990**, *11*, 440.
(41) Pirrung, M.C.; Nunn, D.S. *Tetrahedron Lett.* **1992**, *33*, 6591.
(42) Based on an $[\alpha]_D$ − 190.6° (c = 0.1, CH_3OH) for synthetic and an $[\alpha]_D$ − 202° (c = 0.3, CH_3OH)[33] for natural (−)-LL-C10037α.