New Stereoselective Route to the Epoxyquinol Core of Manumycin-Type Natural Products. Synthesis of Enantiopure (+)-Bromoxone, (−)-LL-C10037α, and (+)-KT 8110

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A practical route is decribed for the preparation of the C_7N core of manumycin-type compounds. Starting from *p*-benzoquinone, optically pure compounds in both forms can be prepared via enzymatic resolution of a derived diacetoxy conduritol. A diepoxy aminoinositol is accessible which can function for formation of enantiopure epoxyquinones and quinols. Examples are given for acylation reactions of this amine with several acyl derivatives. With this approach (−)-LL-C10037α and quinones such as (+)-KT-8110 with 5*R*,6*S*-configuration can be synthesized through oxidation. In addition a short route to (+)-bromoxone is described. Most steps include simple epoxide formation and cleavage reactions which all can be carried out in a high stereoselective manner.

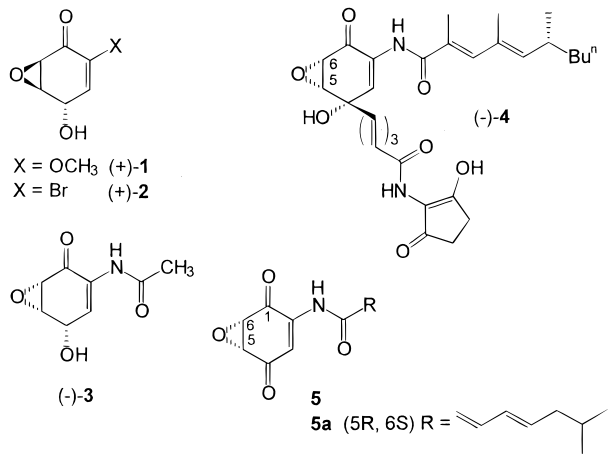
Introduction

There are many natural products with antibiotic and antitumor activity whose common feature is a highly oxygenated cyclohexenone central unit. These compounds have been isolated from various organisms such as fungi, bacteria, and worms. Representative simple examples are molecules such as chaloxone[1] (**1**), bromoxone (**2**), and the *Streptomycetes* metabolite LL-C10037α (**3**) (Scheme 1). Bromoxone (**2**) and its acetate were isolated by Higa and co-workers from marine acon worm in 1987.[2] Lee and co-workers isolated **3** from *Streptomyces* LL-C10037, and the correct structure was determined by Gould et al.[3]

The amido−epoxycyclohexenone core of **3** is also characteristic for more than 20 manumycin-type compounds, for example, manumycin A (**4**), manumycins B−G, asukamycin, and alisamycin.[4] Manumycins have been identified as potent and selective inhibitors of the Ras farnesyltransferase.[5] Their activity depends on the cylohexenone epoxide central unit and the "eastern" side chain resembling the farnesyl group. The "southern" triene chain and the amide-bound C_5N unit do not seem crucial, since oxidized degradation products such as **5** with various "eastern" chains are still active as pharmacophores. (+)-KT 8110 (**5a**) derived by Uosaki et al. by CrO_3 oxidation of isolated EI-1511-3 shows inhibitory potency to interleukine converting enzyme (ICE).[6]

The absolute configuration for the C_7N core of the isolated metabolites is not uniform for all compounds.

Scheme 1



Whereas the oxirane moiety is 5*R*,6*S* in manumycin A (**4**), it is 5*S*,6*R* in alisamycin.[4] The absolute configuration of **5a** was determined as 5*R*,6*S* by CD spectroscopy.[6]

Synthetic compounds **5**, in both enantiomeric forms, were of interest for structural determination of the isolated natural products and were crucial for the preparation of complex molecules such as **4**.

Two similar approaches to racemic antibiotic **3** and related stuctures **5** have been reported,[7,8] and one route toward (−)-LL-C10037α has been described.[9] Recently Taylor[10] developed a strategy to generate enantiopure quinones such as **5** (with 5*S*,6*R*-configuration) and synthesized the enantiomer of **3** ((+)-MT 35214). Applying this process together with a method to introduce "southern" side chains, they achieved the synthesis of (+)-**4** and revised the reported structure of manumycin A to have a *syn*-hydroxy epoxide arrangement.[11] Quinones **5** with 5*R*,6*S*-configuration have not been reported as synthetic compounds yet.

(1) Fex, T.; Wickberg, B. *Acta Chem. Scand.* **1981**, *B35*, 97.
(2) Higa, T.; Okuda, R. K.; Severns, R. M.; Scheur, P. J.; He, C.-H.; Changfu, X.; Clardy, J. *Tetrahedron* **1987**, *43*, 1063.
(3) (a) Lee, M. D.; Fantini, A. A.; Morton, G. O.; James, J. C.; Borders, D. B.; Testa, R. T. *J. Antibiot.* **1984**, *37*, 1149. (b) Shen, B.; Whittle, Y. G.; Gould, S. J.; Keszler, D. A. *J. Org. Chem.* **1990**, *55*, 4422.
(4) See recent reviews: (a) Taylor, R. J. K.; Alcaraz, L.; Kampfer-Eyer, I.; Macdonald, G.; Wie, X.; Lewis, N. *Synthesis* **1998**, 775. (b) Sattler, I.; Thiericke, R.; Zeeck, A. *Nat. Prod. Rep.* **1998**, 221 and references therein.
(5) (a) Hara, M.; Akasaka, K.; Akinaga, S.; Okabe, M.; Nakano, H.; Gomez, R.; Wood, D.; Uh, M.; Tamanoi, F. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 2281. (b) Hara, M.; Han, M. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 3333.
(6) Uosaki, Y.; Agatsuma, T.; Tanaka, T.; Saitho, Y. *J. Antibiot.* **1996**, *49*, 1079, 1085.
(7) Taylor, R. J. K.; Mcdonald, G.; Lewis, N. J.; Kampfer, I. *Tetrahedron Lett.* **1996**, *37*, 2101.
(8) Wipf, P.; Kim, Y. *J. Org. Chem.* **1994**, *59*, 3518.
(9) Wipf, P.; Kim, Y.; Jahn, H. *Synthesis* **1995**, 1549.
(10) Macdonald, G.; Alcaraz, L.; Lewis, N.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 5433.

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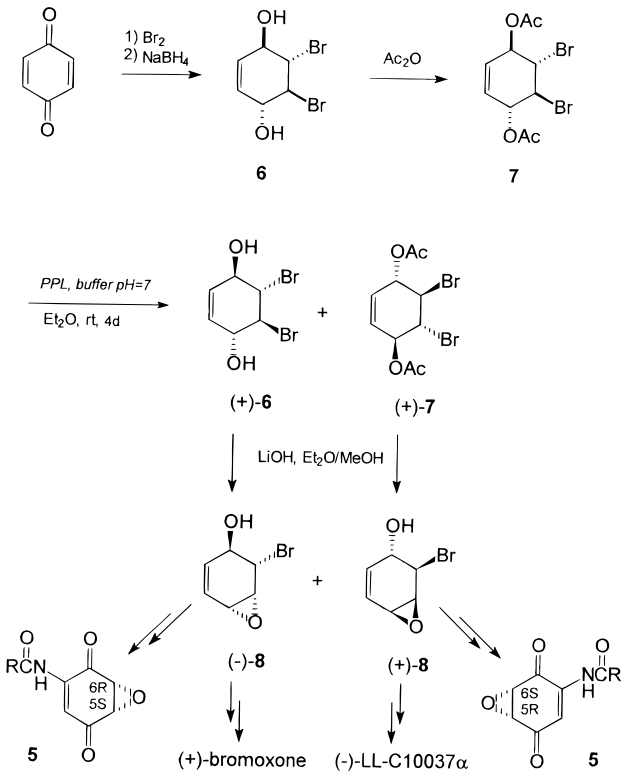
Scheme 2



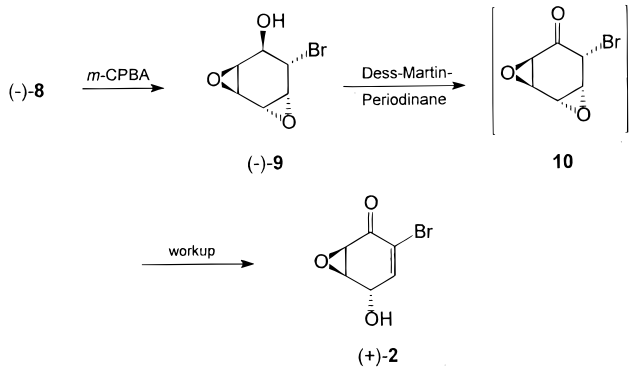
On the other hand, synthetic (±)-bromoxone is known,[12] and Johnson[13] reported the synthesis of enantiopure (+)- and (−)-bromoxone starting from *p*-benzoquinone and subsequent enzymatic resolution related to the method also developed by us.[14,15]

We hereby report a novel highly stereocontrolled route to (+)-bromoxone (**2**), (−)-LL-C10037α (**3**), and (+)-KT 8110 (**5a**) by enzymatic resolution of the diacetate **7** and use of the epoxide (+)- or (−)-**8** as a versatile building block in preparation of the epoxyketone core. (+)-KT 8110 derived by us is the first example of synthetic enantiopure diketone **5** with 5*R*,6*S*-configuration.

Results and Discussion

Dibromodiol **6** can be obtained from *p*-benzoquinone in two steps which yield 90% of an isomeric mixture containing 80−90% of the all-trans isomer (Scheme 2). Acetylation[16] of **6** and recrystallization from ethanol gives pure diacetate **7** on a multigram scale (68%). Hydrolysis of **7** is described by Johnson with lipase Amano PS-30 in buffer pH 8 at 50 °C (16 h). Under these conditions diacetate (+)-**7** is formed in 26% (≥98% ee) and diol (+)-**6** in 47% (90% ee) yield.[13] Our initial attempts to resolve the C_2-symmetric diol **6** by enzymatic esterification with various enzymes were unsatisfactory.[15] However, hydrolysis of racemic diacetate **7** with PPL in phosphate buffer at pH 7.0 in the presence of Et_2O improved the yield and selectivity. The hydrolysis stopped after 50% conversion (4 days) and proceeded with excellent enantioselectivity for both the remaining diacetate (+)-**7** and the resulting diol (+)-**6**. Due to the different solubility in CH_2Cl_2, (+)-**7** can easily be separated from (+)-**6**, and both were obtained in 38% yield and ee > 99% after recrystallization ((+)-**7** from EtOH, (+)-**6** from toluene).

Scheme 3



The absolute configuration of diacetate (+)-**7** was established by an X-ray structure determination. The crystals examined possessed a chiral space group, and the absolute structure parameter of 0.01(4) shows the (+)-isomer to be 1*S*,2*R*,3*R*,4*S*.[14] The following syntheses of natural products confirm the absolute stereochemistry of (+)-**6** and (+)-**7** independently.

Epoxide (−)-**8** can be prepared from diol (+)-**6** by use of LiOH as a weak base in Et_2O/MeOH in high yield (90%). Under the same conditions rapid hydrolysis of diacetate (+)-**7** occurs, and formation of (+)-**8**[17] is observed.

To synthesize (+)-bromoxone, alcohol (−)-(**8**) was epoxidized by *m*-CPBA to give the diepoxide (−)-(**9**) exclusively in a stereoselective manner as expected following Henbest's rule (Scheme 3).[18] According to the synthesis of chaloxone (**1**) described by Fex,[19] oxidation of (−)-**9** should yield (+)-bromoxone in one step. Indeed this transformation succeeded with Dess−Martin periodinane (DMP)[20] to give (+)-**2** in 52% yield. The spectral data of the obtained solid correspond to those observed by Johnson[13] and Higa.[2] The intermediate diepoxyketone **10** resulted from oxidation of DMP can be detected by NMR spectroscopy. **10** is stable under the weak acidic reaction conditions, but any kind of workup gives the rearranged product **2** via β-elimination involving the oxirane ring.

In the synthesis of antibiotic (−)-LL-C10037α (**3**), epoxide (+)-**8** was selectively opened with NaN_3 in allylic position to form azide (−)-**11**[21] (Scheme 4). (−)-**11** is transformed to only one epoxidized product by using *m*-CPBA.[22] Compound **11** was less reactive toward

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(12) Gautier, E. C. L.; Lewis, N.; McKillop, A.; Taylor, R. J. K. *Tetrahedron Lett.* **1994**, *35*, 8759.
(13) Johnson, C. R.; Miller, M. W. *J. Org. Chem.* **1995**, *60*, 6674.
(14) Adelt, S.; Plettenburg, O.; Stricker, R.; Reiser, G.; Altenbach, H.-J.; Vogel, G. *J. Med. Chem.* **1999**, *42*, 1262.
(15) Altenbach, H.-J. In *Antibiotics and Antiviral Compounds*; Krohn, K., Kirst, H., Maas, H., Eds.; VCH Verlagsgesellschaft mbH: Weinheim, 1993; pp 359−372.
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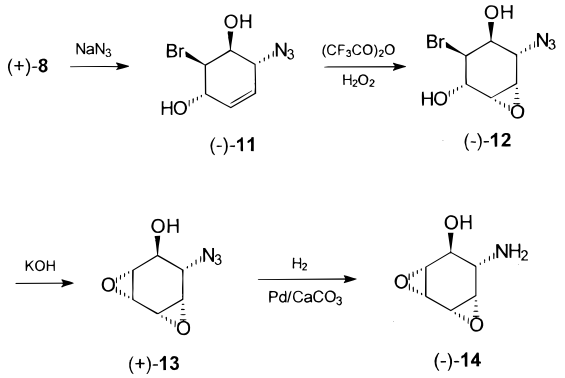
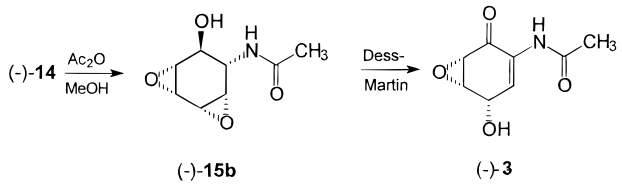
(17) See also: (a) Johnson, C. R.; Miller, M. W. *J. Org. Chem.* **1998**, *63*, 5088. (b) Koreeda, M.; Yoshihara, M. *J. Chem. Soc., Chem. Commun.* **1981**, 974.
(18) Henbest, H. B.; Nicholls, B. *J. Chem. Soc.* **1957**, 4608.
(19) Fex, T. *Tetrahedron Lett.* **1981**, *22*, 2707.
(20) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(21) For racemic **11** see: Zipperer, B.; Hunkler, D.; Fritz, H.; Rihs, G.; Prinzbach, H. *Angew. Chem.* **1984**, *96*, 296.
(22) For a related reaction see: Zipperer, B.; Müller, K.-H.; Gallenkamp, B.; Hildebrand, R.; Fletschinger, M.; Burger, D.; Pillat, M.; Hunkler, D.; Knothe, L.; Fritz, H.; Prinzbach, H. *Chem. Ber.* **1988**, *121*, 757.

Scheme 4



Scheme 5



m-CPBA than **8**; thus, long reaction times and incomplete turnover, even with an excess of oxidizing agent, compelled us to use the more potent trifluoroperoxoacetic acid.[23] We observed much shorter reaction times but no decrease in selectivity. Only one product was formed as a colorless solid in 82% yield (after recrystallization). The expected *syn*-epoxidation of **11** should lead to the correct stereochemistry of natural product **3**. Indeed, the relative stereochemistry of epoxide **12** was established by an X-ray stucture determination of a racemic sample of **12**, which contains two chemically identical molecules in the asymmetric unit.

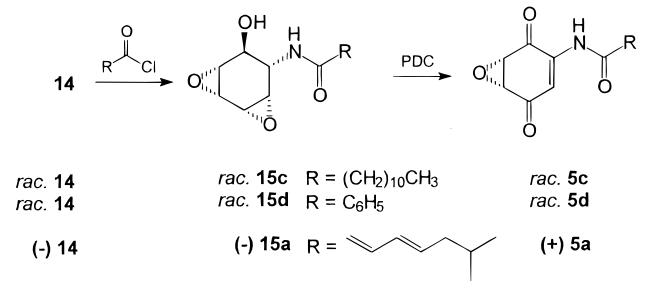
Reaction of epoxide (−)-**12** under basic conditions with KOH in methanol caused the formation of the second epoxide ring to give (+)-**13**. Palladium-catalyzed reduction of this azide leads to amine (−)-**14** as a colorless solid in 79% yield from (+)-**13**.

Introduction of an *N*-acetyl moiety, required for the synthesis of the antibiotic **3**, is carried out by reaction of the amino alcohol (−)-**14** with acetic anhydride in methanol (Scheme 5). The use of methanol as solvent causes complete differentiation between the amino and the hydroxy functions. A doubly acetylated product was not observed. The acetamide (−)-**15b** obtained by this procedure was expected to fulfill the stereochemical requirements for reaction via an oxidation process to (−)-LL-C10037α.

Indeed, reaction with DMP resulted in oxidation and elimination to give the target molecule **3** (α^{25}_D −194 (*c* 1.1, MeOH); for natural **3**[3b], α^{25}_D −202 (*c* 0.3, MeOH)). The spectroscopic data of **3** confirmed the stereochemistry of LL-C10037α reported by Wipf[9] and Gould.[3b] In contrast to oxidation of alcohol **9**, compound **15b** allows only 1 equiv of oxidizing reagent as β-elimination starts already under the reaction conditions. With an excess of periodinane the epoxyquinone resulting from oxidation of the allylic hydroxy group in **3** can be detected.[24]

In an attempt to obtain the natural product **3**, aqueous workup of the reaction mixture led to complete loss of the epoxyquinol compound because of its high water solubility and instability under basic conditions.[8] However, direct chromatography of the crude reaction mixture on silica gel gave a white powder which was still contaminated with aromatic compounds from the oxidizing reagent, but a second chromatography and crystallization gave pure (−)-**3** in 52% yield.

Scheme 6



The amino alcohol **14** is available in both enantiomeric forms (**(−)-14** from **(+)-8**, **(+)-14** from **(−)-8**) as stable solids. Amine **14** can function as a precursor for the formation of manumycin-type compounds containing different amido side chains. Both enantiomers can be used in the synthesis of degradation products such as **5** (Schemes 1 and 6), and these quinones can be converted to manumycins of type **4**. In addition, the saturated primary amino group in **14** seems to be a better nucleophile in coupling reactions with acid chlorides or acid anhydrides than the enamine derivatives described in the literature. The problem of chemoselectivity in the acylation reaction can be solved by using alcohol as the solvent or reaction of 1 equiv of acyl donor in CH_2Cl_2. For example, it was easily possible to synthesize the lauroyl- and benzoylamides **15c** and **15d** in racemic form (80−90% yield), which can be transformed by PDC oxidation to the known[4a] diketone derivatives **5c** and **5d** (65−75% yield).

Using **(−)-** or **(+)-14** and acid chlorides of the naturally occurring eastern side chains of manumycin-type compounds, we were able to obtain enantiopure diketones by oxidation. For example, by coupling of an acid chloride,[25] corresponding to the amido group reported for KT-8110, with **(−)-14**, we prepared enantiopure amide **(−)-15a**. The acid chloride was used as an *E*/*Z* mixture, but recrystallization from EtOAc gave pure (−)-**15a** in 73% yield. Finally, oxidation with PDC transforms (−)-**15a** to quinone (+)-**5a** (yellow solid, mp 125−127 °C). The data of the product (α^{25}_D +54 (*c* = 0.12, MeOH)) are in agreement with those reported by Uosaki[6] (α^{25}_D +53.5 (*c* = 0.12, MeOH)), so the 5*R*,6*S*-configuration was confirmed by our synthetic route.

All amides **15a**−**d** prepared, in racemic or enantiopure form, were crystalline solids sparingly soluble in organic solvents, especially EtOAc, and can be crystallized from

(23) Bartlett, P. A.; McQuaid, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 7855.

(24) Problems can occur with attempts to use 1 equiv of DMP. The reactivity of DMP is observed to vary from preparation to preparation of this reagent. To obtain the best yields, the oxidation reaction of amide **15b** must be calibrated with the applied DMP, respectively. For information about the quality and reactivity of DMP, see: (a) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549. (b) Stevenson, P. J.; Treacy, A. B.; Nieuwenhuyzen, M. *J. Chem. Soc., Perkin Trans. 2* **1997**, 589.

(25) Preparation of the methyl ester: Takacs, J. M.; Jaber, M. R.; Clement, F.; Walters, C. *J. Org. Chem.* **1998**, *63*, 6757. The *E*/*Z* mixture (90:10) was enriched to 97:3 by column chromatography (SiO_2, CH/EtOAc (93:7)) and transformed to the corresponding acid by THF/H_2O/LiOH reflux, 8 h, 90%.

EtOAc or mixtures of EtOAc and MeOH. Water-insoluble amides were filtered from the reaction mixture after addition of water and EtOAc. The quinones **5** prepared by oxidation with PDC were analytically pure as raw products, which need no further purification.

Conclusion

We have successfully developed a new route to the amido−epoxycylohexenone core (C_7N) of manumycin-type natural products. We use the effective and large-scale enzymatic resolution of diacetate **7** and further stereoselective transformations to attain amine **14**, which is available in both enantiomeric forms (five steps (38%) from (+)-**7** or (+)-**6**). Various acylations of **14** have been carried out, and the resulting amides **15** represent the C_7N unit with "eastern side chains" after oxidation. With this methodology we were able to prepare quinones **5** with 5*R*,6*S*-configuration, the synthesis of which has not been reported previously. The preparation of (+)-KT 8110 (**5a**) and (−)-LL-C10037α (**3**) verifies our strategy toward compounds with this absolute configuration.

Experimental Section

General Procedures. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts are quoted in parts per million using the solvent as the internal standard. For interpretation of ^1H spectra ψt (pseudo triplet) for unresolved dd is used. Peak assignments are derived from DEPT and two-dimensional NMR experiments. IR spectra were obtained in KBr, and only noteworthy absorptions (cm^{-1}) are listed. Column chromatography was performed on Merck silica gel 60 (260−400 mesh). All organic extracts were dried over Na_2SO_4, filtered, and concentrated with a rotary evaporator under reduced pressure. Only distilled solvents were used.

(+)-(1*R*,2*S*,3*S*,4*R*)-2,3-Dibromocyclohex-5-ene-1,4-diol, (+)-6, and (+)-(1*S*,2*R*,3*R*,4*S*)-1,4-Diacetoxy-2,3-dibromocyclohex-5-ene, (+)-7. Powdered racemic diacetate **7** (100.0 g, 0.28 mol) and pig pancreas lipase (54.7 g, type II from Sigma-Aldrich Chemie GmbH) were suspended in 1.2 L of phosphate buffer (pH 7, 0.1 M) and 120 mL of diethyl ether. The mixture was stirred vigorously for 4 d. EtOAc (500 mL) was added, and the enzyme was filtered over a pad of Celite. The residue was washed with EtOAc (4 × 150 mL) and water (4 × 150 mL). The combined aqueous layers were extracted with EtOAc (3 × 150 mL). The organic solution was evaporated, and the resulting solid was suspended in CH_2Cl_2 (600 mL). Diol (+)-**6** remains insoluble as a white crystalline solid, while diacetate (+)-**7** dissolves totally. The solid is filtered off and recrystallized from toluene to yield (+)-**6** (28.9 g, 38%): mp 164−165 °C (lit.[13] mp 164−166 °C); α^{25}_D +49.5 (*c* 1.22, acetone); ee > 99%; ^1H NMR (DMSO-d_6) δ 4.13 (AA′, 2H, H-2, H-3), 4.28 (BB′, 2H, H-1, H-4), 5.58 (XX′, 2H, H-5, H-6), 5.67 (d, 2H, J = 6.3 Hz, OH); ^{13}C NMR (DMSO-d_6) δ 61.4 (C-2, C-3), 72.1 (C-1, C-4), 130.4 (C-5, C-6). Anal. Calcd for $C_6H_8Br_2O_2$ (271.93): C, 26.50; H, 2.97. Found: C, 26.74; H, 2.97.

The CH_2Cl_2 layer was evaporated, and the resulting solid was recrystallized from EtOH to give (+)-**7** (37.9 g, 38%) as colorless needles: mp 107−109 °C (lit.[13] mp 107−109 °C); α^{25}_D +11.3 (*c* 5.1,CH_2Cl_2); ee > 99% (chiral HPLC: Whelk, S,S, heptane/2-propanol (90:10), flow 0.8 mL/min) t = 9.08 min (other enantiomer (−)-**7**, t = 10.24 min)); ^1H NMR ($CDCl_3$) δ 2.13 (s, 6H), 4.28 (XX′, 2H, H-2, H-3), 5.69 (BB′, 2H, H-1, H-4), 5.75 (AA′, 2H, H-5, H-6); ^{13}C NMR ($CDCl_3$) δ 20.7, 52.7 (C-2, C-3), 73.4 (C-1, C-4), 128.2 (C-5, C-6), 169.7. Anal. Calcd for $C_{10}H_{12}Br_2O_4$ (356.01): C, 33.74; H, 3.40. Found: C, 33.68; H, 3.39.

(1*S*,2*R*,3*S*,6*S*)-2-Bromo-7-oxabicylo[4.1.0]hept-4-en-3-ol, (+)-8. A solution of diacetate (+)-**7** (6.0 g, 16.9 mmol, 180 mL of Et_2O/MeOH (3:1)) and LiOH (810 mg, 33.8 mmol) was stirred for 45 min at 10 °C, and then further LiOH (400 mg, 16.7 mmol) was added and allowed to react for an additional 30 min. After the reaction was completed, brine/water (2:1) and Et_2O were added, and the aqueous layer was extracted with Et_2O. The organic solution was concentrated under reduced pressure to a small volume and extracted with Et_2O and brine for a second time. Drying and evaporation of solvent gave (+)-**8** (2.90 g, 90%) as a awhite solid. For an analytical sample recrystallization from $CHCl_3$/hexane (1:1) yielded pure (+)-**8** as white needles: mp 114−116 °C (lit.[17a] mp 114−115 °C); α^{25}_D + 172 (*c* 0.37, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.66 (d, 1H, OH, J = 4.5 Hz), 3.51 (dψt, 1H, J = 3−4, 2 Hz, H-6), 3.75 (dd, 1H, J = 4.0, 0.7 Hz, H-1), 4.05 (dd, 1H, J = 8.7, 0.9 Hz, H-2), 4.49 (m, 1H, H-3), 5.93 (dψt, 1H, J = 9.9, 2−3 Hz), 6.06 (dψt, 1H, J = 9.6, 3−4 Hz); ^{13}C NMR ($CDCl_3$) δ 51.6 (C-6), 55.3 (C-1), 55.5 (C-2), 71.2 (C-3), 123.4, 134.8. Anal. Calcd for $C_6H_7BrO_2$ (191.02): C, 37.73; H, 3.69. Found: C, 38.00; H, 3.71.

(1*R*,2*S*,3*R*,6*R*)-2-Bromo-7-oxabicylo[4.1.0]hept-4-en-3-ol, (−)-8. A solution of diol (+)-**6** (4.58 g, 16.9 mmol) was allowed to react under the same conditions described for (+)-**7** to give (−)-**8** (2.9 g, 90%). Recrystallization from $CHCl_3$/hexane (2:1) gave pure (−)-**8** (white needles): mp 114−116 °C; α^{25}_D −172 (*c* 0.36, $CHCl_3$). Anal. Calcd for $C_6H_7BrO_2$ (191.02): C, 37.73; H, 3.69. Found: C, 37.73; H, 3.49.

(1*R*,2*S*,4*R*,5*R*,6*S*,7*R*)-6-Bromo-3,8-dioxatricylo[5.1.0.0^{2,4}]-octan-5-ol, (−)-9. Epoxide (−)-**8** (1.20 g, 6.28 mmol, 50 mL of CH_2Cl_2) was stirred with an excess of *m*-CPBA at room temperature. After the reaction was completed (TLC), EtOAc, saturated $NaHCO_3$, and $Na_2S_2O_3$ were added, and the organic layer was extracted with saturated $NaHCO_3$, saturated NH_4-Cl, and brine. Drying and evaporation gave a white solid (1.10 g, 85%). Recrystallization from CCl_4/$CHCl_3$ (5:4) yielded pure (−)-**9** (870 mg, 67%) as colorless needles: mp 135−136 °C; α^{25}_D −203 (*c* 1.0, acetone); ^1H NMR ($CDCl_3$) δ 2.65 (d, 1H, J = 4.6 Hz, OH), 3.41 (d, 1H, J = 4.1 Hz), 3.54 (d, 1H, J = 4.0 Hz), 3.64 (dd, 1H, J = 4, 2.3 Hz), 3.66 (dd, 1H, J = 4.3, 2.4 Hz), 4.23 (AB, 2H, H-5, H-6); ^{13}C NMR ($CDCl_3$) δ 51.9 (C-6), 52.4, 55.2, 55.2, 56.3, 71.1 (C-5). Anal. Calcd for $C_6H_7BrO_3$ (207.02): C, 34.81, H, 3.41. Found: C, 35.07; H, 3.43. Data for racemic **9** (white solid): mp 97−98 °C (CCl_4/$CHCl_3$ (6:4)). Anal. Calcd for $C_6H_7BrO_3$ (207.02): C, 34.81; H, 3.41. Found: C, 34.78; H, 3.36.

Bromoxone, (+)-2. To a solution of diepoxide (−)-**9** (330 mg, 1.59 mmol, 20 mL of CH_2Cl_2) at 0 °C was added Dess−Martin periodinane (1.5 g, 3.54 mmol) in one portion. After 30 min the mixture was allowed to warm to room temperature and stirring continued for 2 h. EtOAc was added, and the solution was washed quickly with saturated $NaHCO_3$ (containing solid $Na_2S_2O_3$), saturated NH_4Cl, and brine. Drying and concentration gave a brown solid (253 mg, 77%). Recrystallization from CCl_4/$CHCl_3$ (1:1) yielded (+)-**2** (170 mg, 52%, yellow needles): mp 131−132 °C (lit.[13] mp 138−139 °C); α^{25}_D +203 (*c* 2.5, acetone); ^1H NMR (acetone-d_6) δ 3.63 (dd, 1H, J = 3.6, 1.3 Hz, H-1), 3.84 (m, 1H, H-6), 4.70 (br s, 1H, H-5), 5.14 (br s, 1H, OH), 7.23 (dd, 1H, J = 5.2, 2.3 Hz, H-4); ^{13}C NMR (acetone-d_6) δ 54.8 (C-1), 59.3 (C-6), 65.9 (C-5), 123.3 (C-3), 147.6 (C-4), 188.2 (C-2). Anal. Calcd for $C_6H_5BrO_3$ (205.00): C, 35.15; H, 2.46. Found: C, 35.33; H, 2.48. Data for racemic **2** (yellow needles): mp 92−93 °C (CCl_4/$CHCl_3$ (6:4)). Anal. Calcd for $C_6H_5BrO_3$ (205.00): C, 35.15; H, 2.46. Found: C, 35.00; H, 2.48.

(1*S*,2*R*,3*S*,6*R*)-6-Azido-2-bromocyclohex-4-ene-1,3-diol, (−)-11. A solution of NaN_3 (5.1 g, 78 mmol) and NH_4Cl (1.9 g, 35 mmol) in MeOH/H_2O (50 mL, 8:1) at 0 °C was treated with epoxide (+)-**8** (3.0 g, 15.7 mmol, 12 mL THF). After 1.5 h solid NH_4Cl was added and the mixture concentrated under reduced pressure. To the resulting solution were added brine and EtOAc, and the aqueous layer was washed several times with EtOAc. The organic layers were dried and concentrated to give a yellow oil (3.7 g, 100%). Recrystallization from CCl_4/$CHCl_3$ (1:1) yielded pure (−)-**11** (2.9 g, 78%, white needles): mp 82−83 °C; α^{25}_D −146 (*c* 1.1, acetone); ^1H NMR (acetone-d_6) δ 4.02 (m, 1H, H-1), 4.12 (m, 1H, H-6), 4.28 (ψt, 1H, J = 2−4 Hz, H-2), 4.49 (m, 1H, H-3), 4.79 (d, 1H, J = 6.1 Hz, OH-3), 4.88 (d, 1H, J = 5.4 Hz OH-1), 5.72 (dd, 1H, J = 10.1, 2.5

Hz, H-5), 5.91 (dddd, 1H, J = 10.1, 3.9, 1.7, 1.0 Hz, H-4); ^{13}C NMR (acetone-d_6) δ 60.1 (C-2), 63.8 (C-6), 71.2 (C-1), 71.6 (C-3), 127.5 (C-5), 131.3 (C-4); IR (KBr) 2090 cm^{-1} (N_3). Anal. Calcd for $C_6H_8BrN_3O_2$ (234.05): C, 30.79; H, 3.45; N, 17.95. Found: C, 30.57; H, 3.47; N, 18.31. Data for racemic **11** (light yellow crystals): mp 96−97 °C ($CHCl_3$). Anal. Calcd for $C_6H_8BrN_3O_2$ (234.05): C, 30.79; H, 3.45; N, 17.95. Found: C, 30.75; H, 3.53; N, 18.10.

(1*S*,2*S*,3*S*,4*S*,5*R*,6*S*)-5-Azido-3-bromo-7-oxabicylo[4.1.0]heptane-2,4-diol, (−)-12. To alkene (−)-**11** (2.0 g, 8.55 mmol, 50 mL of CH_2Cl_2) was added a freshly prepared solution of trifluoroperacetic acid[23] (from TFAA (4.3 mL, 6.5 g, 30.9 mmol) and H_2O_2 (85%, 1.0 mL, 30 mmol) in 15 mL of CH_2Cl_2) dropwise at 0 °C over 2 h. Then the solution was allowed to warm to room temperature. After the end was determined by TLC (ca. 1 h), the reaction mixture was slowly added to a cooled and stirred solution of 7 g of $NaHCO_3$ in 100 mL of brine and 150 mL of EtOAc. After addition of $Na_2S_2O_3$ the organic layer was washed with $NaHCO_3$, NH_4Cl, and brine and then dried. Evaporation of the solvent gave a yellow solid (2.10 g, 99%). Recrystallization from $CHCl_3$ yielded colorless needles (1.72 g, 81%): mp 95−96 °C; α^{25}_D −115 (*c* 1.1, acetone); ^{1}H NMR (acetone-d_6) δ 3.45 (ψt, 1H, J = 3−4 Hz, H-1), 3.58 (ψt, 1H, J = 3−4 Hz, H-6), 3.95 (dψt, 1H, H-4), 4.03 (dd, 1H, J = 6.5, 2.9 Hz, H-5), 4.11 (dd, 1H, J = 4.5, 2.2 Hz, H-3), 4.41 (m, 1H, H-2), 4.58 (d, 1H, J = 7.5 Hz, OH-2), 4.86 (d, 1H, J = 5.4 Hz, OH-4); ^{13}C NMR (acetone-d_6) δ 55.7 (C-1), 56.5 (C-6), 59.8 (C-3), 63.4 (C-5), 70.4 (C-4), 71.2 (C-2); IR (KBr) 2090 cm^{-1} (N_3). Anal. Calcd for $C_6H_8BrN_3O_3$ (250.05): C, 28.82; H, 3.22; N, 16.80. Found: C, 28.65; H, 3.16; N, 17.12. Data for racemic **12** (colorless crystals): mp 83−84 °C ($CHCl_3$). Anal. Calcd for $C_6H_8BrN_3O_3$ (250.05): C, 28.82; H, 3.22; N, 16.80. Found: C, 28.68; H, 3.23; N, 17.11.

(1*S*,2*R*,4*R*,5*S*,6*S*,7*S*)-6-Azido-3,8-dioxatricylo[5.1.0.0^{2,4}]octan-5-ol, (+)-13. A solution of (−)-**12** (2.20 g, 8.80 mmol) and KOH (5% in MeOH, 15 mL) was stirred for 2 h at 0 °C, then further KOH (10% in MeOH, 7 mL) was added, and the reaction mixture was stirred for another 1 h at 0 °C. Solid NH_4Cl, brine, and EtOAc were added, and the mixture was extracted three times with EtOAc. Drying and concentration gave a white solid (1.46 g, 100%). Recrystallization from $CHCl_3$ yielded pure (+)-**13** (1.29 g, 84%) as colorless needles: mp 119−120 °C; α^{25}_D +8.6 (*c* 1.3, acetone); ^{1}H NMR (acetone-d_6) δ 2.97 (dd, 1H, J = 4.0, 1.2 Hz, H-4), 3.27 (d, 1H, J = 3.8 Hz, H-7), 3.38 (dd, 1H, J = 4.0, 2.6 Hz, H-2), 3.45 (ψt, 1H, H-1), 3.73 (m, 1H, H-5), 3.86 (d, 1H, J = 9.6 Hz, H-6), 5.05 (d, 1H, J = 5.8 Hz, OH); ^{13}C NMR (acetone-d_6) δ 49.2 (C-1), 50.1 (C-2), 56.3 (C-4), 56.7 (C-7), 65.2 (C-6), 70.9 (C-5); IR (KBr) 2100, 2080 cm^{-1} (N_3). Anal. Calcd for $C_6H_7N_3O_3$ (169.13): C, 42.61; H, 4.17; N, 24.84. Found: C, 42.70; H, 4.28; N, 24.74. Data for racemic **13** (light yellow needles): mp 92−93 °C ($CHCl_3$). Anal. Calcd for $C_6H_7N_3O_3$ (169.13): C, 42.61; H, 4.17; N, 24.84. Found: C, 42.99; H, 4.17; N, 25.14.

(1*S*,2*R*,4*R*,5*S*,6*S*,7*S*)-6-Amino-3,8-dioxatricylo[5.1.0.0^{2,4}]octan-5-ol, (−)-14. Azide (−)-**13** (1.10 g, 6.50 mmol, 100 mL of dry EtOH) was stirred with Lindlar catalyst (250 mg, Pd/$CaCO_3$, Pd 5%) in an atmosphere of H_2 for 6−8 h at room temperature. The solution was filtered two times (folded filters) and the residue washed with EtOH (200 mL). Concentration to a small amount of EtOH caused crystallization of (−)-**14** as colorless needles (870 mg, 79%): mp 130 °C dec; α^{25}_D −44 (*c* 1.50, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.63 (br s, 2 H, NH_2), 2.86 (dd, 1H, J = 3.9, 1.4 Hz, H-4), 2.92 (dd, 1H, J = 8.6, 1.5 Hz, H-6), 3.08 (dd, 1H, J = 3.7, 1.3, H-7), 3.27 (dd, 1H, J = 8.6, 1.3 Hz, H-5), 3.36 (dd, 1H, J = 3.8, 2.8 Hz, H-2), 3.38 (m, 1H, H-1), 5.28 (br s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ 47.4 (C-1), 48.5 (C-2), 52.5 (C-6), 54.4 (C-4), 56.4 (C-7), 70.0 (C-5). Anal. Calcd for $C_6H_9NO_3$ (143.14): C, 50.35; H, 6.34; N, 9.79. Found: C, 50.31; H, 6.37; N, 9.76. Data for racemic **14** (colorless crystals): mp 134−135 °C dec. Anal. Calcd for $C_6H_9NO_3$ (143.14): C, 50.35; H, 6.34; N, 9.79. Found: C, 50.28; H, 6.33; N, 9.71.

(1*S*,2*R*,4*R*,5*S*,6*S*,7*S*)-*N*-(6-Hydroxy-3,8-dioxatricylo-[5.1.0.0^{2,4}]oct-5-yl)acetamide, (−)-15b. To amino alcohol (−)-**14** (105 mg, 0.73 mmol, 4 mL of MeOH) was added Ac_2O (150 μL, 162 mg, 1.59 mmol) dropwise at 0 °C over 10 min. The mixture was stirred for 30 min and allowed to warm to room temperature. Concentration under reduced pressure gave a white solid (136 mg, 99%). Recrystallization from EtOAc/MeOH (2:1) yielded pure (−)-**15b** (110 mg, 81%) as colorless needles: mp 147−148 °C dec; α^{25}_D −97 (*c* 2.6, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.85 (s, 3H), 2.92 (dd, 1H, J = 4.1, 1.4 Hz, H-7), 3.11 (dd, 1H, J = 3.9, 1.6 Hz, H-4), 3.41 (dd, 1H, J = 4.0, 2.8, H-1), 3.44 (ψt, 1H, H-2), 3.49 (ddd, 1H, J = 9.1, 6.1, 1.5 Hz, H-6), 4.06 (m, 1H, H-5), 5.31 (d, 1H, J = 6.0 Hz, OH), 7.85 (d, 1H, J = 7.9 Hz, NH); ^{13}C NMR (DMSO-d_6) δ 23.2, 48.4 (C-2), 48.9 (C-1), 50.9 (C-5), 55.1 (C-7), 55.5 (C-4), 67.2 (C-6), 170.2. Anal. Calcd for $C_8H_{11}NO_4$ (185.17): C, 51.89; H, 5.99; N, 7.56. Found: C, 51.70; H, 5.97; N, 7.43. Data for racemic **15b** (colorless crystals): mp 142−143 °C dec (EtOAc/MeOH (1:1)). Anal. Calcd for $C_8H_{11}NO_4$ (185.17): C, 51.89; H, 5.99; N, 7.56. Found: C, 51.73; H, 5.76; N, 7.20.

LL-C10037α, (−)-3. To a solution of amide **15b** (53 mg, 0.286 mmol, 6 mL of dry CH_2Cl_2) was added 1 equiv of Dess−Martin periodinane at 0 °C. After being stirred for 30 min at 0 °C, the mixture was allowed to warm to room temperature and stirred for 1 h. MeOH (200 μL) was added, and column chromatography (silica gel, CH_2Cl_2/MeOH (90:10)) gave a white solid (86 mg). A second purification by column chromatography (silica gel, EtOAc) yielded fractions containing pure (−)-**3**. By concentration under reduced pressure to a small amount of solvent, pure (−)-**3** (27 mg, 52%) precipitated as colorless needles: mp 146−148 °C dec; α^{25}_D −194 (*c* 1.1, MeOH) (lit.[3b] α^{25}_D −202 (*c* 0.3, MeOH)); ^{1}H NMR (DMSO-d_6) δ 2.00 (s, 3H), 3.53 (d, 1H, J = 4.3 Hz, H-1), 3.76 (dψt, 1H, J = 4.3 Hz, H-6), 4.79 (dψt, 1H, J = 6.3 Hz, H-5), 5.72 (d, 1H, J = 6.3 Hz, OH), 7.05 (ψt, 1H, H-4), 8.96 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 23.6, 52.1 (C-1), 53.6 (C-6), 63.3 (C-5), 128.2 (C-3), 128.2 (C-4), 169.4, 189.5 (C-2). Anal. Calcd for $C_8H_9NO_4$ (183.16): C, 52.46; H, 4.95; N, 7.65. Found: C, 52.67; H, 4.99; N, 7.47. Data for racemic **3** (colorless crystals): mp 161−163 °C dec (lit.[9] mp 167 °C dec). Anal. Calcd for $C_8H_9NO_4$ (183.16): C, 52.46; H, 4.95; N, 7.65. Found: C, 52.62; H, 4.97; N, 7.42.

Preparation of Water-Insoluble Amides 15a,c,d. General Procedures. To amine **14** (1 mmol, 10 mL CH_2Cl_2) and Et_3N (1.5 mmol) was added a solution of acid chloride (1 mmol, 2 mL of CH_2Cl_2) over 5 min at 0 °C. After the mixture was stirred for 5 h at 0 °C, water and EtOAc were added, and the resulting precipitate was filtered off and washed with water and EtOAc. The filtrate was diluted with 100 mL of EtOAc or CH_2Cl_2, extracted with brine, and dried. Concentration gave a white solid (80−90%, together with precipitate). Recrystallization from EtOAc or mixtures of EtOAc and MeOH yielded pure amide **15a,c,d** (70−80%).

Dodecanoic Acid (6-Hydroxy-3,8-dioxatricyclo[5.1.0.0^{2,4}]oct-5-yl)amide, 15c: white solid (77%); mp 169−171 °C (EtOAc); ^{1}H NMR (DMSO-d_6) δ 0.82 (t, 3H, J = 6.8 Hz, H-12), 1.21−1.26 (m, 16H, H-4 to H-11), 1.46 (m, 2H, H-3), 2.08 (t, 2H, J = 7.4 Hz, H-2), 2.89 (dd, 1H, J = 4.0, 1.3 Hz H-7′), 3.06 (dd, 1H, J = 3.9, 1.6 Hz, H-4′), 3.38 (ψt, 1H, H-1′), 3.41 (ψt, 1H, H-2′), 3.47 (ψt, 1H, H-6′), 4.05 (m, 1H, H-5′), 5.25 (d, 1H, J = 5.5 Hz, OH), 7.70 (d, 1H, J = 8.0 Hz, NH); ^{13}C NMR (DMSO-d_6) δ 13.8 (C-12), 22.0, 25.1, 28.5, 28.6, 28.7, 28.8, 28.9, 28.9, 31.2, 35.2, 47.7 (C-2′), 48.2 (C-1′), 50.0 (C-5′), 54.4 (C-7′), 54.7 (C-4′), 66.4 (C-6′), 172.5 (C-1); MS (EI) m/z 325 (M$^+$; 4), 57 ($C_4H_9^+$; 100). Anal. Calcd for $C_{18}H_{31}NO_4$ (325.44): C, 66.43; H, 9.60; N, 4.30. Found: C, 66.35; H, 9.44; N, 4.24.

***N*-(6-Hydroxy-3,8-dioxatricyclo[5.1.0.0^{2,4}]oct-5-yl)benzamide, 15d:** white solid (73%); mp 167−171 °C (EtOAc/MeOH (1:1)); ^{1}H NMR (DMSO-d_6) δ 2.96 (dd, 1H, J = 4.0, 1.4 Hz H-7), 3.21 (dd, 1H, J = 4.0, 1.5 Hz, H-4), 3.42 (dd, 1H, J = 4.0, 2.7 Hz H-1), 3.47 (ψt, 1H, H-2), 3.75 (ddd, 1H, J = 9.3, 6.1, 1.4 Hz H-6), 4.31 (dψt, 1H, H-5), 5.35 (d, 1H, J = 6.1 Hz, OH), 7.41−7.52 (m, 3H, ArH), 7.82−7.88 (m, 2H, ArH), 8.27 (d, 1H, J = 8.0 Hz, NH); ^{13}C NMR (DMSO-d_6) δ 47.7 (C-2), 48.3 (C-1), 51.1 (C-5), 54.7 (C-7), 55.0 (C-4), 66.0 (C-6), 127.3, 128.1, 131.2, 134.2, 166.5; MS (EI) m/z 247 (M$^+$; 1), 105 ($C_6H_5CO^+$; 100). Anal. Calcd for $C_{13}H_{13}NO_4$ (247.26): C, 63.15; H, 5.30; N, 5.66. Found: C, 62.89; H, 5.25; N, 5.82.

(1*S*,2*R*,4*R*,5*S*,6*S*,7*S*)-7-Methylocta-2(*E*),4(*E*)-dienoic Acid (6-Hydroxy-3,8-dioxatricyclo[5.1.0.0^{2,4}]oct-5-yl)amide, (−)-15a. To a solution of 7-methylocta-2(*E*),4(*E*)-dienoic acid[25] (97% purity, 97 mg, 0.63 mmol, 1 mL of dry benzene and traces of pyridine) was added oxalyl chloride (300 μL, 3.5 mmol) at 5 °C. After the end of gas evolution (20 min) the mixture was heated for 15 min at 40 °C and then evaporated to dryness under reduced pressure. The crude precipitate was dissolved in CH_2Cl_2 and allowed to react under conditions described in the General Procedures (see above) to give a white solid (73%): mp 163−165 °C (EtOAc); α^{25}_D −43 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 6H, J = 6.6 Hz, H-8), 1.70 (nonet, 1H, J = 6.7 Hz, H-7), 2.05 (m, 2H, H-6), 3.27 (H (ψt, 1H), 3.30 (m, 1H), 3.53−3.55 (m, 2H), 4.05 (br s, H-6′), 4.66 (m, 1H, H-5′), 4.83 (br s, 1H, OH), 5.81 (d, 1H, J = 15.1 Hz, H-2), 6.09−6.16 (m, 2H, H-4, H-5), 6.30 (d, 1H, J = 8.7 Hz, NH), 7.17 (m, 1H, J = 15.1, 10.0 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 22.3 (C-8), 28.3 (C-7), 42.3 (C-6), 47.7, 48.1 (C-5′), 48.7 (C-4′), 48.9, 52.6 (C-7′), 67.2 (C-6′), 121.0 (C-2), 129.2, 142.3 (C-3), 143.0, 166.7 (C-1); MS (EI) *m*/*z* 279 (M^+; 9), 137 (100). Anal. Calcd for $C_{15}H_{21}NO_4$ (279.35): C, 64.49; H, 7.58; N, 5.01. Found: C, 64.58; H, 7.43; N, 4.88.

Preparation of Quinones. General Procedures. A suspension or solution of diepoxy amide **15** (0.25 mmol, 25 mL of CH_2Cl_2) and PDC (3 mmol) was heated under reflux for 4−8 h. After the reaction was completed (TLC), the mixture was filtered and the filtrate was washed two times with 0.5 M HCl. The organic layers were dried and filtered over a short column of Al_2O_3 (neutral, activity V). Concentration under reduced pressure gave pure quinones **5** (65−75%) which can be crystallizated by addition of methyl *tert*-butyl ether.

2-Lauramido-5,6-epoxy-1,4-benzoquinone, 5c: white solid (71%); mp 107−108 °C (108 °C).[4a] Anal. Calcd for $C_{18}H_{27}NO_4$ (321.41): C, 67.26; H, 8.47; N, 4.36. Found: C, 67.09; H, 8.37; N, 4.64. Further data are in accord with the literature.[4a]

2-Benzamido-5,6-epoxy-1,4-benzoquinone, 5d: yellow solid (73%); mp 110−111 °C (111−112 °C).[4a] Anal. Calcd for $C_{18}H_{27}NO_4$ (321.41): C, 64.20; H, 3.73; N, 5.67. Found: C, 64.11; H, 3.75; N, 5.87. Further data are in accord with the literature.[4a]

(5*R*,6*S*)-2-(7-Methylocta-2(*E*),4(*E*)-dienamido)-5,6-epoxy-1,4-benzoquinone, (+)-5a: yellow solid (64%); mp 125−127 °C; α^{25}_D +54 (*c* 0.12, MeOH) (lit.[5] α^{25}_D +53.5 (*c* 0.12, MeOH)); ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 6H, J = 6.6 Hz, H-8′), 1.74 (nonet, 1H, J = 6.7 Hz, H-7′), 2.09 (m, 2H, J = 6.5 Hz, H-6), 3.83 (dd, 1H, J = 3.6, 2.4 Hz H-5), 3.92 (d, 1H, J = 3.8, H-6), 5.91 (d, 1H, J = 15.0 Hz, H-2′), 6.15−6.23 (m, 2H, H-4′, H-5′), 7.33 (m, 1H, J = 15.0, 10.0 Hz, H-3′), 7.62 (d, 1H, J = 2.2 Hz, H-3), 7.85 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 22.3 (C-8′), 28.2 (C-7′), 42.4 (C-6′), 52.5 (C-6′), 53.9 (C-5), 115.3 (C-3), 120.0 (C-2′), 128.9, 139.0 (C-2), 145.5, 145.9, 165.0, 188.2, 191.0; MS (EI) *m*/*z* 275 (M^+; 23), 137 (100). Anal. Calcd for $C_{15}H_{17}NO_4$ (275.32): C, 65.44; H, 6.23; N, 5.09. Found: C, 65.66; H, 6.33; N, 4.95.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **9**, **12**−**15**, **2**, **3**, **5a**, and **10** ($CDCl_3$ solution with DMP) and X-ray data for compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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