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Singlet Oxygen in Synthesis. Formation of Antimycin A_3 from an Oxazole Template

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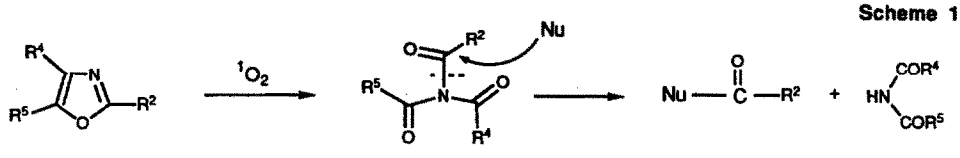
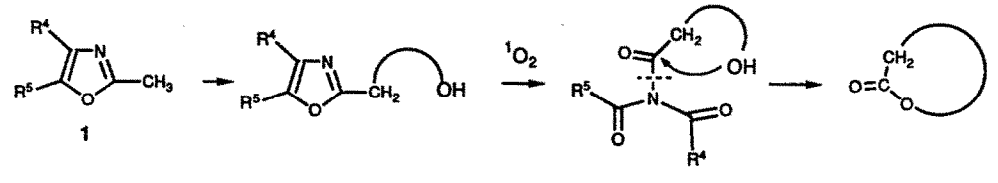
Abstract: Antimycin A_3 has been synthesized using an oxazole template for constructing the framework of the dilactone. Formation of the nine-membered ring was accomplished by reaction of an ω-hydroxyl group with an activated carboxylate generated in the reaction of the oxazole with singlet oxygen.

In previous publications,[1] we have reported that the reactions of substituted oxazoles with singlet oxygen under mild conditions lead to complex rearrangements with the formation of triamides in nearly quantitative yields. The triamides represent activated forms of each of the carbonyl groups, since nucleophilic attack at such sites generates good leaving groups, as shown in Scheme 1. We have also found that in the intramolecular reactions of triamides with nucleophiles, acyl carbonyls usually react more readily than the aroyl counterparts, permitting selectivity in the use of the triamide as an activated form of the acyl carboxylate.[1g] Thus, starting with 2-methyl-4,5-diphenyl oxazole **1**, an ω-hydroxyl group may be introduced at the 2-position by suitable alkylation. Subsequent dye-sensitized photooxidation of the oxazole nucleus generates a triamide which then undergoes macrolactone formation as illustrated in Scheme 2.[1b]

Scheme 1

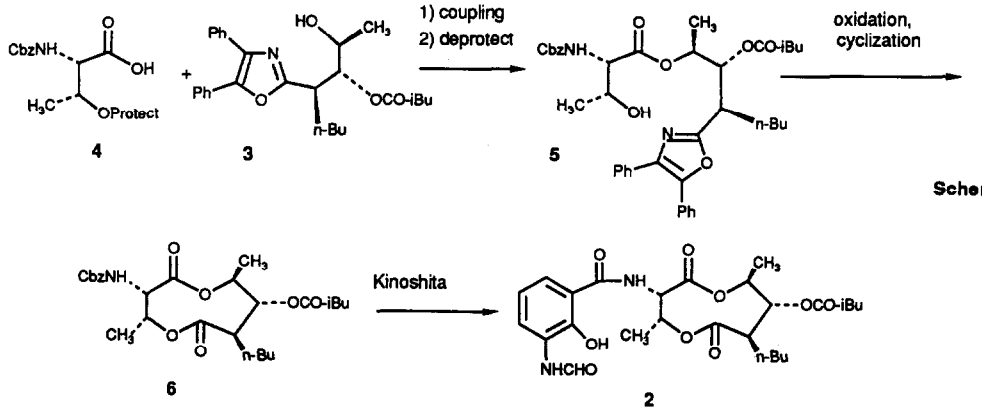


Scheme 2



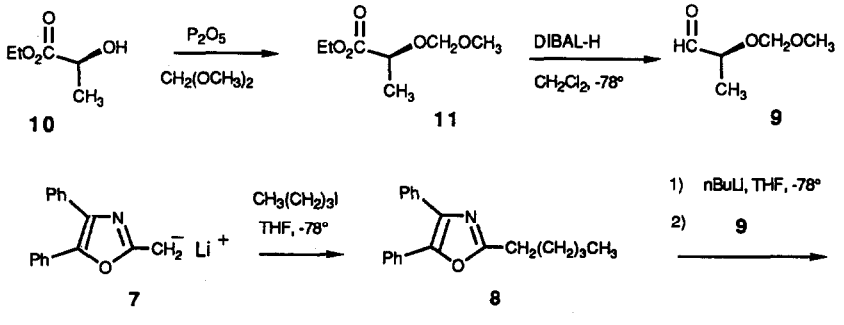
In recent years, we have used this methodology for the synthesis of a series of naturally occurring macrolides including antimycin A_3, **2**, an antibiotic and antifungal agent isolated from a number of streptomyces strains.[2] In this report, we describe the details of our antimycin synthesis in which 2-methyl-4,5-diphenyl oxazole **1** is used as a template for protection/activation of the latent acyl carboxyl group at the oxazole 2-carbon. In our overall synthetic strategy, we envisioned a coupling of the substituted oxazole segment **3** with a suitably protected form of N-benzyloxycarbonyl-L-(+)-threonine **4** by esterification to form **5**. Photooxygenation-cyclization would then lead to the polyfunctional chiral nine-membered dilactone **6**, which has previously been converted to (+)-antimycin A_3[2] (Scheme 3).[3]

Dedicated with respect and admiration to Professor Lars Skattebøl on the occasion of his 65th birthday

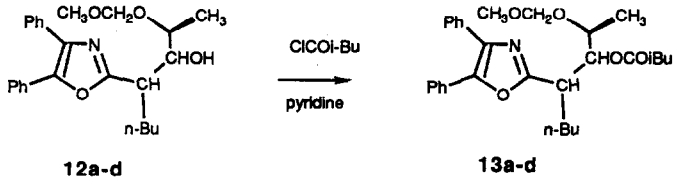


Scheme 3

In accord with our earlier studies on electrophilic additions to the lithium anion of 2-methyl-4,5-diphenyloxazole (**7**), the n-butyl group at C-7 of antimycin A_3 (Kinoshita nomenclature) was introduced by reaction of **7** with 1-iodobutane in THF at -78 °C to give 2-*n*-pentyl-4,5-diphenyloxazole (**8**) (93%).[4] The entire carbon skeleton of the "right half" of **2** would then be accessible via an aldol type condensation with a properly protected derivative of L-(+)-lactaldehyde. For our purposes, we chose S-2-methoxymethyloxypropanal (**9**), obtained from ethyl L-(+)-lactate (**10**) by a) treatment with dimethoxymethane and phosphorus pentoxide in CH_2Cl_2[5] to provide ethyl S-(-)-2-methoxymethyloxypropanoate (**11**) (84%) and b) reduction with diisobutylaluminum hydride in CH_2Cl_2 at -78 °C (52%). Metalation of the alkylated oxazole **8** with *n*-butyllithium in THF as before, followed by addition of aldehyde **9** produced a mixture of four possible diastereomers (at C-7 and C-8) in 58% overall yield. HPLC analysis indicated a mixture of alcohols **12a-d** in a ratio of 4:3:2:1, the major isomer of which, **12a**, was separable by repeated chromatography. On a preparative scale, it proved expedient to acylate the mixture **12a-d** with isovaleryl chloride in dry pyridine (2 days, room temperature) to the corresponding esters **13a-d** (74%) which were isolated cleanly by chromatography (Scheme 4).

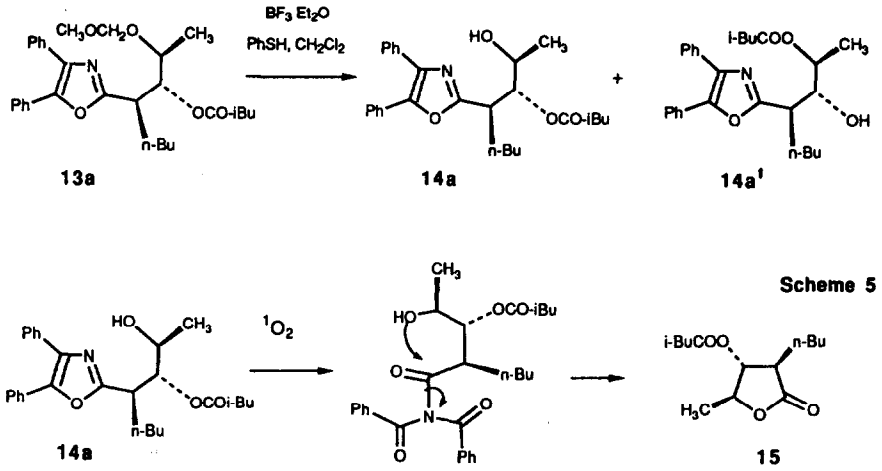


Scheme 4



We were pleased to find that the alcohol **12a** which predominated in the aldol addition of **8** to **9** had the desired configuration corresponding to that of the natural product. As outlined below, we were able to show that **12a** could be converted through **13a** and **14a** to (+)-blastmycinone (**15**) of known absolute configuration. Furthermore, it was shown that pure diastereomeric alcohol **12a** could be independently transformed to the acylated derivative **13a** (isovaleryl chloride, DMAP, pyridine, 21%), without epimerization during the acylation step.

Initially, removal of the MOM ether group with catalytic hydrochloric acid in methanol at 60°C resulted in the isolation of the desired diastereomer **14a** along with the O-acyl migration product **14a'** in an unfavorable 1:2.5 ratio respectively, an effect previously encountered by Kinoshita under basic conditions.[7] This obstacle was surmounted by treatment of ester **13a** with boron trifluoride-etherate and thiophenol in CH_2Cl_2[8] leading to the formation of the desired hydroxy derivative **14a** in 57% yield, with only a trace of O-acyl migration product **14a'**. The absolute stereochemistry of **14a** was firmly established by its conversion to (+)-blastmycinone (**15**),[9] a product of mild saponification of antimycin A_3. Thus, photooxygenation of **14a** (sensitox, CH_2Cl_2, 3h) in the absence of acid catalysis readily produced (+)-blastmycinone (**15**) as the sole isolable lactone species (35%), exhibiting physical and spectroscopic properties (b.p., IR, $[\alpha]_D^{23}$) in close accord with the literature values[3] and a 90 MHz ^1H NMR spectrum which was in essentially complete agreement with a 100 MHz spectrum of the natural material graciously provided by M. Kinoshita.[10] Compound **14a** was thus shown to possess the 7R, 8R, 9S-configuration present in antimycin A_3 (Scheme 5).

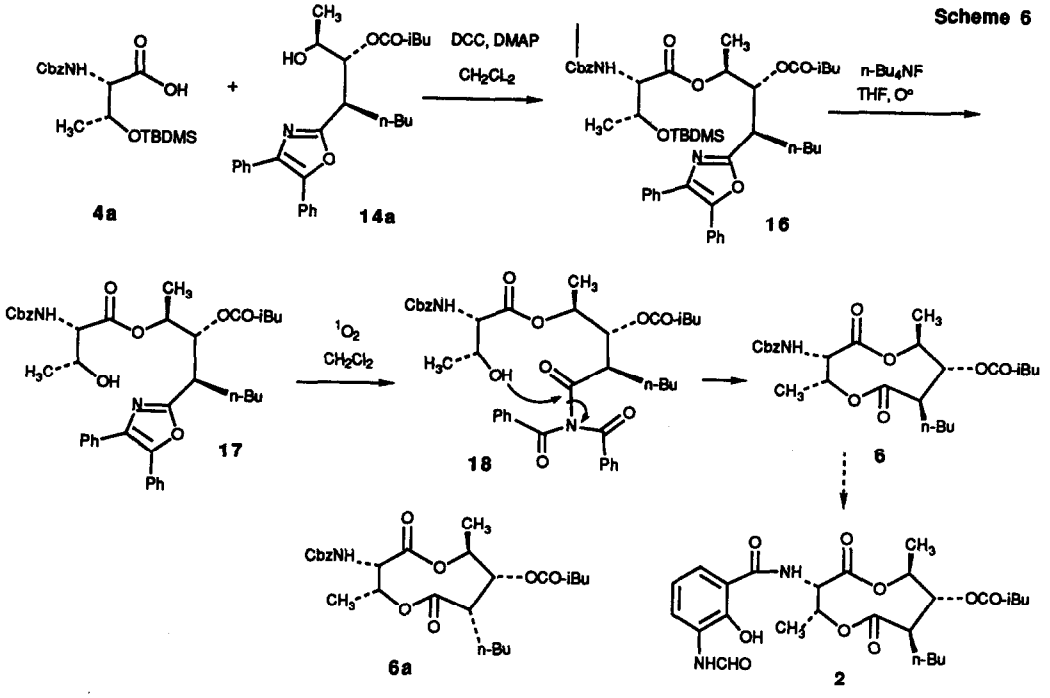


Scheme 5

The γ-hydroxy-oxazole **14a** was then coupled with N-benzyloxycarbonyl-O-t-butyldimethylsilyl-L-threonine (**4a**)[11] using DCC and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2[12] to form the ester **16** (95%). Following desilylation (n-Bu_4NF, THF, 0 °C),[11] the resultant ω-hydroxyoxazole **17** was subjected to dye-sensitized photooxygenation (sensitox, CH_2Cl_2, 3h) affording the triamide **18**, which was not isolated. Macrocyclization was then accomplished by slowly adding a solution of **18** in dry xylenes to a refluxing solution of pyridinium p-toluenesulfonate (catalytic amount)[13] in xylenes over 6h. This procedural modification involving buffered acid catalysis and shorter reaction time was adopted because of the labile isovalerate ester functionality and the observation of epimerization at higher temperatures.[7] Under these conditions, the known nine-membered dilactone[3] **6** was isolated in 20% yield, a modest improvement in overall activation-cyclization for this system.

Compound **6** exhibited physical and spectroscopic properties (m.p., $[\alpha]_D^{22}$, IR, high resolution MS) in complete accord with those values reported by Kinoshita.[7,3] The 100 MHz ^{1}H NMR spectrum was completely superimposable on a spectrum of an authentic sample of this material provided by Dr. Kinoshita.[10] A stereoisomer was also present in the reaction mixture (7%) and may be tentatively assigned the structure of the C-7 epimer **6a** based on comparison with the published report[7] and by a marked downfield shift (~0.4 ppm) of the H-7 ^{1}H NMR signal. Since the intermediate dilactone **6** has previously been converted to (+)-antimycin A_3,[3] our work constitutes a formal synthesis of the naturally occurring macrolide (Scheme 6).

Scheme 6



A salient feature in this preparative pathway is the acyclic esterification through a DCC-activated carboxylate to the protected ω-hydroxyoxazole system (**16**), which is realized quite cleanly, and without interference by the latent activated carboxylate masked in the oxazole nucleus. Other activated carboxylate derivatives (e.g., thio esters, N-acylimidazoles) would suffer from unwanted coupling reactions under these conditions. Furthermore, it appears that the use of pyridinium p-toluenesulfonate instead of the stronger acid, p-toluenesulfonic acid, does not affect the lactonization process adversely, but does provide an alternative for substrates containing acid-sensitive functionality. In the course of the work, it was also shown that the oxazole group is compatible with acylation reaction conditions and deprotection steps using boron trifluoride-etherate and tetra-n-butylammonium fluoride. The strong U.V. absorbance of the oxazole moiety is a valuable asset in both the identification of new compounds by TLC and in their isolation by silica gel chromatography. In addition, the 2-substituted-4,5-diphenyloxazole derivatives show excellent solubility in a wide range of organic solvents, thus rendering them widely useful as templates in such multistep syntheses. We are currently planning to incorporate the unique aspects of this procedure in the synthesis of other naturally occurring macrolides of biological interest.

Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus with open capillary tubes. The ^1H NMR spectra were recorded on a Varian EM-360, a Varian EM-390, a Jeol FX-90Q or a Bruker WM-250 spectrometer. The infrared (IR) spectra were recorded on a Perkin-Elmer 700A spectrophotometer or a Nicolet 7000 or 5SX spectrophotometer (FT). Optical rotations were recorded on a Perkin-Elmer 241 polarimeter in a 1-dcm quartz polarimetry cell. Mass spectra (MS) were obtained on a Hewlett-Packard GC 5840A/MS 5985A system. High resolution mass spectra were performed by Drs. Susan Rottschaefer and Alan Tremper of Smith Kline Corp. or by Dr. Marvin Thompson, University of Connecticut. Elemental analyses were performed by Dr. Robert Rittner, Olin Laboratories, New Haven, Connecticut or at Atlantic Microlab, Inc., Atlanta, Georgia.

2-n-Pentyl-4,5-diphenyloxazole **8**. To a solution of 2-methyl-4,5-diphenyloxazole **1** (16.486 g, 0.070 mol) in 700 mL of THF at -78 °C was added *via* mechanically-driven syringe a 1.10 M solution of n-butyllithium in hexane (70.0 mL, 0.077 mol, 1.1 equiv) over 1.5 h. The resulting carmine red solution was stirred at -78 °C for an additional 20 min, then a solution of 1-iodobutane (7.96 mL, 0.070 mol, 1.0 equiv) in 70 mL of THF was added over 30 min. After stirring at -78 °C for an additional 1 h, the reaction was quenched by the addition of 50 mL of water. The cooling bath was removed, and the solution was allowed to warm to room temperature over 1 h. The reaction mixture was concentrated *in vacuo*, then dissolved in 350 mL of Et_2O and washed with 200 mL of water. The aqueous layer was extracted with 2 x 150 mL portions of Et_2O, then the combined Et_2O extracts were dried over $MgSO_4$ and evaporated *in vacuo* to give a crude yellow oil. Flash chromatography (gradient elution with 94:6 to 92:8 pentane:Et_2O) provided 19.053 g (93%) of **8** (R_f 0.69, 2:1 pentane: Et_2O) as a thick, pale yellow oil. ^1H NMR (250 MHz, $CDCl_3$) δ 7.54-7.72 (m, 4H), 7.25-7.45 (m, 6H), 2.85 (t, J=7.7 Hz, 2H), 1.86 (quin., J=7.5 Hz, 2H), 1.32-1.54 (m, 4H), 0.93 (t, J=7.0 Hz, 3H). MS (20 eV), m/z (relative %) 292 (22.8), 291 (M^+, 91.9), 262 (26.0), 249 (28.8), 248 (81.2), 236 (18.8), 235 (100.0, base), 165 (23.0), 149 (16.6), 105 (21.0), 104 (16.1), 103 (21.8), 84 (10.9).

HRMS calcd for $C_{20}H_{21}NO$ 291.1623, found 291.1624.

Ethyl S-(-)-2-methoxymethyloxypropanoate **11**. To a stirred solution of ethyl L-(+)-lactate **10** (Sigma Chem. Co., 10.00 mL, 88.2 mmol) in 350 mL of CH_2Cl_2 were added dimethoxymethane (methylal, 350 mL, 3.96 mol, 45 equiv) and phosphorus pentoxide (~200 g) at room temperature. The mixture was periodically agitated manually over 2 h, then was poured slowly into 150 mL of ice-cooled saturated Na_2CO_3 (aq). The remaining solid residue was transferred by careful rinsing with an additional 250 mL of cold saturated Na_2CO_3 (aq). The phases were separated, and the aqueous layer was further extracted with 200 mL of Et_2O. The combined organic extracts were washed with 200 mL of saturated NaCl (aq), dried over $MgSO_4$ and evaporated *in vacuo* to give a pale yellow oil. High vacuum distillation provided 11.99 g (84%) of **11** as a clear, colorless oil. bp 39°C (0.35 mm Hg). $[\alpha]_D^{22}$ -88.1° (c 2.85, $CHCl_3$). IR ($CDCl_3$) 1745 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 4.62 (ABq, J= 4.5 Hz (calcd), 2H), 4.14 (q, J= 6.9 Hz, 1H), 4.13 (q, J= 7.1 Hz, 2H), 3.32 (s, 3H), 1.36 (d, J= 6.9 Hz, 3H), 1.22 (t, J= 7.1 Hz, 3H).

Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.68; H, 8.73.

S-2-methoxymethyloxypropanal **9**. To a solution of ester **11** (8.109 g, 0.50 mol) in 65 mL of CH_2Cl_2 at -78°C was added via syringe a 0.96 M solution of diisobutylaluminum hydride in hexane (titrated by the method

of D.E. Jordon *Anal. Chem.* **1968**, *40*, 2150; 52.1 mL, 0.050 mol, 1.00 equiv) over 20 min. The reaction mixture was stirred for an additional 1h at -78 °C, then was quenched by the addition of 13 mL of cold saturated NH_4Cl(aq). A solution of 26 mL of 4% HCl (aq) was subsequently added, the cooling bath was removed, and the mixture was allowed to warm to room temperature over 30 min. The resulting dense, white slurry was extracted with 4 x 50 mL portions of CH_2Cl_2, then the combined CH_2Cl_2 extracts were dried over Na_2SO_4 and evaporated *in vacuo* to give a crude, light yellow oil. Due to the instability and hygroscopic tendencies of the product, the material was handled under nitrogen or argon whenever possible and a small amount of hydroquinone (5 mg) was added as a stabilizer. Distillation under reduced pressure provided 3.094 g of **9** (52%) as a clear, colorless oil. The material was used in the next step (*vide infra*) immediately and without further purification. bp 43°C (17 mm Hg). ^{1}H NMR (90 MHz, $CDCl_3$) δ 9.64 (d, J= 1.6 Hz, ~1H), 4.74 (s, 2H), 4.03 (dq, J= 1.6, 7.0 Hz, 1H), 3.42 (s, 3H), 1.32 (d, J= 7.0 Hz, 3H). The aldehyde **9** was fully categorized as the 2,4-dinitrophenylhydrazone adduct, according to the following procedure.

S-(-)-2-methoxymethyloxypropanal-(2,4-dinitrophenyl)-hydrazone). To a sample of crude (undistilled) S-2-methoxymethyloxypropanal **9** (190 mg, 1.61 mmol), prepared as above, was added a solution of 2,4-dinitrophenylhydrazine (~0.50 g) in 5 mL of 95% EtOH and 1 mL of water at room temperature. After stirring at room temperature for 6 h, the reaction was directly subjected to flash chromatography (gradient elution with 9:1 to 8:2 pentane:Et_2O) to give a crude yellow solid. Recrystallization from Et_2O/pentane provided 92 mg (19%) of the title compound (R_f 0.49, 1:1 Et_2O:pentane) as bright yellow plates. mp 83.0-83.5°C. $[\alpha]_D^{21}$ -96.1° (c 2.00, $CHCl_3$). IR ($CHCl_3$) 3350, 2425, 1625, 1602 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.01 (br s, 1H), 9.10 (d, J= 2.6 Hz, 1H), 4.70 (ABq, J= 8.1 Hz (calcd), 2H), 4.45 (dq, J= 6.5, 6.2 Hz, 1H), 3.40 (s, 3H), 1.44 (d, J=6.6Hz, 3H). MS (20eV), m/z (relative %) 299 (11.6), 298 (M^+, 84.5), 249 (23.8), 237 (81.2), 236 (100.0, base), 223 (33.0), 203 (19.6), 194 (10.2), 193 (11.3), 177 (32.7), 117 (15.9), 87 (53.4), 69 (94.2).

HRMS calcd. for $C_{11}H_{14}N_4O_6$: 298.0913, found 298.0919.

Anal. Calcd for $C_{11}H_{14}N_4O_6$: C, 44.30; H, 4.73; N, 18.78. Found: C,44.26; H, 4.74; N, 18.77.

2-(1-n-Butyl-2-hydroxy-3-methoxymethyloxybutyl)-4,5-diphenyloxazole **12a-d**. To a solution of 2-n-pentyl-4,5-diphenyloxazole **8** (7.628 g, 26.18 mmol) in 260 mL of THF at -78 °C was added via syringe a 1.10 M solution of n-butyllithium in hexane (26.18 mL, 28.8 mmol, 1.1 equiv) over 45 min. The resulting carmine red solution was stirred at -78 °C for an additional 20 min, then a solution of S-2-methoxymethyloxypropanal **9** (3.09 g, 26.18 mmol) in 25 mL of THF was added over 20 min. After stirring at -78 °C for an additional 30 min, the reaction was quenched by the addition of 25 mL of saturated NH_4Cl (aq). The cooling bath was removed, and the solution was allowed to warm to room temperature over 1 h. The reaction mixture was concentrated *in vacuo*, then dissolved in 300 mL of Et_2O and washed with 200 mL of water. The aqueous layer was extracted with 2 x 200 mL portions of Et_2O, then the combined Et_2O extracts were dried over $MgSO_4$ and evaporated *in vacuo* to give a crude red oil. Flash chromatography (gradient elution with 94:6 to 3:2 pentane:Et_2O) provided 6.248 g (58%) of the title compound as a mixture of four diastereomers **12a-d** (R_f 0.42, 0.54, 0.33, 0.48 respectively, 1:1 pentane:Et_2O) as a thick, yellow oil. IR ($CDCl_3$), 3625, 3450 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.53-7.78 (m, 4H), 7.25-7.48 (m, 6H), 4.53-4.80 (m, 2H), 4.01-4.14 (m, 1H), 3.67-3.87 (m, ~1H), 3.38, 3.37, 3.36, 3.39 (s, total 3H), 3.13-3.31 (m, 1H), 1.80-2.22 (m, 2H), 1.12-1.45 (m, 7H), 0.78-0.98 (m, 3H).

On preparative scale, the mixture of diastereomers **12a-d** was taken on to the next step without further purification (*vide infra*).

Separation of (+)-(1R, 2R, 3S)-2-(1-n-Butyl-2-hydroxy-3-methoxy-methyloxybutyl)-4,5-diphenyloxazole **12a** from the mixture, **12a-d**. A small sample (~350 mg) of the mixture of diastereomers **12a-d** was subjected to repeated flash chromatography (gradient elution with 92:8 to 4:1 pentane:Et_2O) in order to obtain an analytical sample of major diastereomer **12a** (R_f 0.42, 1:1 pentane:Et_2O) as a thick, pale yellow oil. $[\alpha]_D^{21}$ + 0.6° (c 1.06, $CHCl_3$) IR ($CDCl_3$) 3625 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.53-7.72 (m, 4H), 7.23-7.46 (m, 6H), 4.68 (ABq, J= 15.7 Hz (calcd), 2H), 4.00-4.10 (m, 1H), 3.68 (dq, J=5.8, 5.8 Hz, 1H), 3.38 (s, 3H), 3.13-3.26 (m, 1H), 1.82-2.12 (m, 2H), 1.26 (d, J= 6.2 Hz, 3H), 1.14-1.41 (m, 4H), 0.89 (t, J= 6.9 Hz, 3H). MS (20 eV), m/z (relative %) 409 (M^+, 21.2), 364 (18.3), 321 (22.8), 320 (100.0, base), 292 (28.7), 291 (59.6), 290 (22.7), 262 (13.5), 249 (20.1), 248 (75.9).

HRMS calcd for $C_{25}H_{31}NO_4$ 409.2253, found 409.2222.

High performance liquid chromatograpy (HPLC) analysis of the mixture **12a-d**. Analyses were performed using a 3.9 mm x 30 cm μ-porasil column (Waters Assoc., Inc.) with 92:8 hexanes:EtOAc as eluent operating at a flow rate of 7.0 mL/min. The relative ratio of stereoisomers **12a:b:c:d** (as the mixture after preliminary chromatography) at retention times 4.3, 2.6, 5.7 and 3.3 min respectively was 4:3:2:1 (by peak area). After repeated chromatograpy, components **12b** and **12d** could not be separated, but could be positively identified as those peaks at retention times 2.6 and 3.3 min respectively in the mixture. Component **12c** was isolated with some contamination by component **12a**, but could be positively identified as the peak at retention time 5.7 min in the mixture. The major component **12a** was separated most cleanly and was positively identified as the peak at retention time 4.3 min in the mixture. As component **12a** could be directly converted to ester **13a** (*vide infra*), the separation of components **12b-d** was not further studied.

2-(1-n-Butyl-2-isobutylcarbonyloxy-3-methoxymethyloxybutyl-4,5-diphenyloxazole **13a-d**. To a solution of oxazoles **12a-d** (6.24 g, 15.26 mmol) in 30 mL of pyridine at room temperature was added (dropwise) a solution of isovaleryl chloride (5.58 mL, 45.78 mmol, 3.0 equiv) in 35 mL of pyridine over 30 min. A yellow precipitate formed after several min, and the mixture was stirred at room temperature for 24 h. The mixture was then partitioned between 200 mL of water and 350 mL of Et_2O. The aqueous layer was extracted with 2 x 200 mL portions of Et_2O, then the combined Et_2O extracts were washed successively with 2 x 250 mL portions of cold 10% H_2SO_4 (aq), 2 x 250 mL portions of cold saturated $NaHCO_3$(aq) and 300 mL of saturated NaCl(aq). The Et_2O extracts were then dried over $MgSO_4$ and evaporated *in vacuo* to give a crude red oil. Flash chromatography (gradient elution with 93:7 to 3:1 pentane:Et_2O) provided 5.576 g total (74%) of the title compound as a partially separated mixture of four diastereomers **13a-d** (R_f 0.60, 0.54, 0.54, 0.44 respectively, 2:1 pentane:Et_2O). Repeated flash chromatograpy (gradient elution with 93.5:6.5 to 3:1 pentane:Et_2O) of the partially separated components was successful in isolating major component **13a** (R_f 0.60) and component **13d** (R_f 0.44), but components **13b** and **13c** (R_f 0.54, 0.54) were isolated as a mixture.

(+)-(1R, 2R, 3S)-2-(1-n-Butyl-2-isobutylcarbonyloxy-3-methoxymethyl-oxybutyl)-4,5-diphenyloxazole **13a**. Isolated 1.995 g (26%) as a thick, pale yellow oil. R_f 0.60, 2:1 pentane:Et_2O. $[\alpha]_D^{21}$ + 17° (c 0.37, $CHCl_3$). IR ($CDCl_3$) 1745 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.52-7.72 (m, 4H), 7.22-7.43 (m, 6H), 5.50 (dd, J= 4.1, 8.3 Hz, 1H), 4.61 (ABq, J= 19.3 Hz (calcd), 2H), 3.73 (dq, J= 4.2, 6.3 Hz, 1H), 3.32 (s, 3H), 3.20-3.32 (m, 1H), 2.27 (d, J= 6.2 Hz, 2H), 2.05-2.26 (m, 1H), 1.72-1.95 (m, 2H), 1.12-1.38 (m, 4H), 1.18

(d, J= 6.4 Hz, 3H), 0.97 (d, J= 6.5 Hz, 3H), 0.96 (d, J= 6.4 Hz, 3H), 0.87 (t, J= 6.8 Hz, 3H). MS (20 eV), m/z (relative %) 493 (M^+, 4.1), 391 (7.3), 348 (23.9), 347 (29.6), 346 (100.0, base).

HRMS calcd for $C_{30}H_{39}NO_5$ 493.2828, found 493.2832.

Stereoisomer (+)-**13a** could be independently converted to stereoisomer (+)-**14a** (*vide infra*), therefore, similar conversions for compounds **13b-d** were not attempted.

Stereoisomers **13b and 13c**. Isolated 1.205 g (16% overall) as a thick, pale yellow oil. R_f 0.54, 0.54, 2:1 pentane: Et_2O. IR ($CDCl_3$) 1744 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.54-7.70 (m, 4H), 7.28-7.44 (m, 6H), 5.35-5.47 (m, 1H), 4.58-4.84 (ABq, J= 37.8 Hz (calcd), δ 4.73; ABq, J= 14.6 Hz (calcd), δ 4.63; total 2H), 3.70-3.82, 3.86-3.96 (m, total 1H), 3.22-3.56 (m, 1H), 3.31, 3.39 (s, total 3H), 2.11-2.38 (d, J= 6.4 Hz, δ 2.15; d, J= 6 Hz, δ 2.33, total 2H), 1.98-2.30 (m, 1H), 1.63-1.96 (m, 2H), 1.17-1.42 (m, 4H), 1.18-1.22 (d, J= 6.3 Hz, δ 1.20; d, J=6.4 Hz, δ 1.21; total 3H), 0.86-1.01 (d, J= 5.7 Hz, δ 0.99; d, J=6.3 Hz, δ 0.87; total 6H), 0.82-.0.92 (m, 3H).

Stereoisomer **13d**. Isolated 1.296 g (17%) as a thick, pale yellow oil. R_f 0.44, 2:1 pentane:Et_2O. IR ($CDCl_3$) 1744, 1717 sh cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.54-7.72 (m, 4H), 7.23-7.48 (m, 6H), 5.36 (dd, J= 7.5, 3.7 Hz, 1H), 4.69 (ABq, J= 16.3 Hz (calcd), 2H), 3.98 (dq, J= 6.2, 3.7 Hz, 1H), 3.20-3.60 (m, 1H), 3.40 (s, 3H), 2.12 (d, J= 6.7 Hz, 2H), 1.91-2.08 (m, 1H), 1.52-1.90 (m, 2H), 1.14-1.41 (m, 4H), 1.25 (d, J=6.3 Hz, 3H), 0.88 (t, J= 6.8 Hz, 3H), 0.81 (d, J= 6.6 Hz, 3H), 0.77 (d, J=6.5 Hz, 3H).

Independent conversion of (+)-**12a** to (+)-**13a**. To a solution of oxazole **12a** (16 mg, 0.039 mmol) in 0.25 mL of pyridine at room temperature was added *via* syringe isovaleryl chloride (25 μL, 0.20 mmol, 5:1 equiv) over 5 min. A yellow precipitate formed after several min, and the mixture was stirred at room temperature for 24 h. An additional portion of isovaleryl chloride (10μL, 0.08 mmol, 2.1 equiv) was added *via* syringe, and the mixture was stirred for another 24 h. A final portion of isovaleryl chloride (30 μL, 0.25 mmol, 6.4 equiv) and 4-dimethylamino-pyridine (1 mg, 0.008 mmol, 0.2 equiv) were added, and the mixture was stirred for another 18 h. The mixture was then partitioned between 20 mL of water and 25 mL of Et_2O. The aqueous layer was extracted with 2 x 20 mL portions of Et_2O, then the combined Et_2O extracts were washed successively with 2 x 50 mL portions of cold 10% H_2SO_4 (aq), 2 x 40 mL portions of cold saturated $NaHCO_3$ (aq) and 40 mL of saturated NaCl(aq). The Et_2O extracts were dried over $MgSO_4$ and evaporated *in vacuo* to give a crude yellow oil. Flash chromatography (gradient elution with 93:7 to 9:1 pentane:Et_2O) afforded 4 mg (21%) of stereoisomer (+)-**13a** (R_f 0.60, 2:1 pentane:Et_2O) whose 250 MHz ^1H NMR spectrum was completely superimposable on that of (+)-**13a** previously isolated from the mixture.

(+)-(1R, 2R, 3S)-2-(1-n-Butyl-2-isobutylcarbonyloxy-3-hydroxybutyl)-4,5-diphenyloxazole **14a**. To a stirred solution of oxazole ester **13a** (263 mg, 0.533 mmol) and thiophenol (0.27 mL, 2.67 mmol, 5.0 equiv) in 5.5 mL of CH_2Cl_2 at room temperature was added boron trifluoride-etherate (0.20 mL, 1.60 mmol, 3.0 equiv). After stirring at room temperature for 1.5 h, the reaction was quenched by the careful addition of 10 mL of cold saturated $NaHCO_3$ (aq). The reaction mixture was then extracted with 4 x 15 mL portions of $CHCl_3$, and the combined CH_2Cl_2 and $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated *in vacuo* to give a crude yellow oil. Flash chromatography (gradient elution with 93:7 to 85:15 pentane:Et_2O) provided 136 mg (57%) of **14a** (R_f 0.54, 1.1 pentane:Et_2O) as a thick, colorless oil. $[\alpha]_D^{20}$ + 6.1° (c 0.90, $CHCl_3$). IR ($CDCl_3$) 3650, 3475, 1740

cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.53-7.70 (m, 4H), 7.25-7.43 (m, 6H), 5.20 (dd, J= 6.8, 5.2 Hz, 1H), 3.76-3.92 (m, 1H), 3.21-3.33 (m, 1H), 2.95 (d, J=4.9 Hz, 1H), 2.27 (d, J= 6.7 Hz, 2H), 2.04-2.22 (m, 1H), 1.73-2.02 (m, 2H), 1.23-1.41 (m, 4H), 1.18 (d, J= 6.3 Hz, 3H), 0.98 (d, J= 6.4 Hz, 6H), 0.87 (t, J= 6.6 Hz, 3H). MS (20 eV), m/z (relative %) 449 (M^+, 13.9), 347 (16.2), 320 (17.8), 305 (22.0), 304 (100.0, base), 248 (14.4).

HRMS calcd for $C_{28}H_{35}NO_4$ 449.2566, found 449.2568.

A trace (~10 mg, 4%) of the O-acylmigration product **14a'** (see following procedure) was identified in earlier fractions by NMR and TLC.

Attempted conversion of (+)-**13a** to (+)-**14a**. Isolation of the O-acyl migration product **14a'**. A sample of oxazole ester **13a** (652 mg, 1.32 mmol) in 13 mL of a 1% conc HCl in absolute MeOH solution was stirred at 60 °C for 2.5 h. After cooling to room temperature, the reaction mixture was diluted with 250 mL of Et_2O, washed with 150 mL of water, then with 150 mL of saturated $NaHCO_3$ (aq). The Et_2O extract was dried over $MgSO_4$ and evaporated *in vacuo* to produce a crude yellow oil. Flash chromatography (gradient elution with 93:7 to 85:15 pentane:Et_2O) gave 350 mg (59%) of the O-acyl migration product **14a'** (R_f 0.65, 1:1 pentane:Et_2O) as a thick, pale yellow oil. IR ($CDCl_3$) 3650, 3475, 1738 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.53-7.70 (m, 4H), 7.28-7.43 (m, 6H), 4.94 (dq, J= 6.5, 6.2 Hz, 1H), 4.03-4.13 (m, 1H), 3.63 (d, J= 2.9 Hz, 1H), 3.06-3.18 (m, 1H), 2.19 (d, J= 6.0 Hz, 2H), 2.04-2.18 (m, 1H), 1.84-1.96 (m, 2H), 1.33 (d, J= 6.2 Hz, 3H), 1.20-1.42 (m, 4H), 0.97 (d, J= 6.4 Hz, 6H), 0.88 (t, J= 6.8 Hz, 3H). MS (20 eV), m/z (relative %) 449 (M^+, 17.3), 346 (20.0), 321 (21.4), 320 (100.0, base), 304 (17.5), 292 (10.6), 291 (39.2), 290 (13.4), 249 (13.4), 248 (57.6), 105 (11.6), 85 (14.8).

Further elution provided 143 mg (24%) of a second component (R_f 0.54, 1:1 pentane: Et_2O) which could be identified as the desired diastereomer **14a** by NMR and TLC. The ratio of **14a'** to **14a** (by isolation) was therefore 2.5 to 1. Subsequent hydrolytic experiments at lower temperatures and weaker acidic conditions still produced a mixture of these components.

(+)-(2R, 3R, 4S)-2-n-Butyl-4-hydroxy-3-isobutylcarbonyloxypentanoic acid 1,4-lactone, (+)-Blastmycinone **15**. A solution of hydroxyoxazole **14a** (136 mg, 0.303 mmol) in 10 mL of CH_2Cl_2 was oxygenated in the presence of Sensitox (Rose Bengal polymer, 20 mg) during irradiation with a tungsten-halogen light source (650 w) operating at 85V for 3 h. After the Sensitox was removed by filtration, the solvent was evaporated *in vacuo* to give a crude yellow oil-solid mixture. Flash chromatography (gradient elution with 96:4 to 85:15 pentane:Et_2O) gave 27 mg (35%) of **15**(R_f 0.50, 2:1 pentane:Et_2O) as a yellow oil. Further purification by Kugelrohr distillation provided a pure sample as a pale yellow oil which exhibited physical and spectroscopic properties quite comparable to those reported in the literature. bp 170-175 °C (20 mm Hg) [lit, bp 125-130 °C (8 mm Hg)]. $[\alpha]_D^{23}$ + 9.0° (c 1.07, $CHCl_3$) [lit,$[\alpha]_D^{23}$ + 10° (c 1.5, $CHCl_3$)]. IR (CCl_4) 1788, 1748 cm^{-1} [lit, IR (CCl_4) 1782, 1754 cm^{-1}]. ^1H NMR (250 MHz, $CDCl_3$) δ 4.94 (dd, J= 4.8, 5.5 Hz, 1H), 4.37 (dq, J= 4.6, 6.6 Hz, 1H), 2.69 (dt, J= 8.2, 5.7 Hz, 1H), 2.23 (d, J= 6.6 Hz, 2H), 2.03-2.22 (m, 1H), 1.55-1.97 (m, 2H), 1.47 (d, J= 6.6 Hz, 3H), 1.23-1.50 (m, 4H), 0.97 (d, J= 6.5 Hz, 6H), 0.91 (t, J= 7.1 Hz, 3H) [lit, ^1H NMR (100 MHz, $CDCl_3$) δ 4.95 (dd, $J_{2,3}$= 5.8 Hz, 1H), 4.37 (dq, $J_{3,4}$ = 4.5 Hz, 1H), 2.69 (m, 1H), 1.45 (d, $J_{4,\ Me}$ = 6.5 Hz, 3H)]. A 90 MHz ^1H NMR spectrum completely matched a 100 MHz spectrum of the authentic material kindly provided by M. Kinoshita.[10]

(+)-N-Benzyloxycarbonyl-0-t-butyldimethylsiyl-L-threonine **4a**. A mixture of N-benzyloxycarbonyl-L-(+)-threonine (Sigma Chem. Co., 6.330 g, 25.00 mmol), t-butyldimethylsilyl chloride (4.250 g, 28.25 mmol, 1.13 equiv) and imidazole (3.745 g, 55.00 mmol, 2.20 equiv) in 5.0 mL of dimethylformamide was stirred at 35°C for 18 h. The reaction mixture was concentrated *in vacuo* then dissolved in 200 mL of Et_2O and washed with 150 mL of *cold* saturated $NaHCO_3$ (aq), then with 150 mL of water. The Et_2O extract was then dried over Na_2SO_4 and evaporated *in vacuo* to give a crude white solid. Flash chromatography (gradient elution with 96:4 to 9:1 CH_2Cl_2: MeOH) yielded 5.836 g (64%) of **4a** (R_f 0.63, 9:1 CH_2Cl_2:MeOH) as a white crystalline solid. Recrystallization from Et_2O/pentane provided an analytical sample as clear, colorless plates. mp 154-157°C. $[\alpha]_D^{22}$ + 10.5° (c 1.69, $CHCl_3$). IR ($CDCl_3$) 3475, 3050 br, 1738, 1727, 1718 sh cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, chloroform standard) δ 7.35 (brs, 5H), 5.49 (d, J= 8.3 Hz, 1H), 5.12 (s, 2H), 4.42-4.53 (m, 1H), 4.31 (dd, J= 2.0, 8.4 Hz, 1H), 1.19 (d, J= 6.3 Hz, 3H), 0.84 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). MS (20 eV), m/z (relative %) 367 (M^+, 0.3) 310 (6.2), 266 (8.7), 160 (6.9), 159 (47.0), 115 (7.4), 103 (6.9), 92 (9.3), 91 (100.0, base), 73 (12.5).

HRMS calcd for $C_{18}H_{29}NO_5Si$ 367.1815, found 367.1802.

Anal. Calcd for $C_{18}H_{29}NO_5Si$: C, 58.83, H, 7.95; N, 3.81. Found: C, 58.95; H, 8.00; N, 3.78.

(-)-(1R, 2R, 3S)-2-(3-(N-Benzyloxycarbonyl-0-t-butyldimethylsilyl-L-threonyloxy)-1-n-butyl-2-isobutylcarbonyloxybutyl)-4,5-diphenyloxazole **16**. A mixture of (+)-benzyloxycarbonyl-0-t-butyldimethylsilyl-L-threonine **4a** (1.308 g, 3.56 mmol, 3.00 equiv), hydroxyoxazole **14a** (5.33 mg, 1.19 mmol), N,N'-dicyclohexylcarbodiimide (734 mg, 3.56 mmol, 3.00 equiv) and 4-dimethylaminopyridine (43 mg, 0.35 mmol, 0.30 equiv) in 10 mL of CH_2Cl_2 was stirred at room temperature with a white precipitate forming within several h. After it was stirred at room temperature for 24 h, the reaction mixture was diluted with 75 mL of anhydrous Et_2O, filtered and evaporated *in vacuo* to produce a crude yellow oil. Flash chromatography (gradient elution with 94:6 to 9:1 pentane: Et_2O) provided 903 mg (95%) of **16** (R_f 0.62, 2:1 pentane:Et_2O) as a colorless glass. $[\alpha]_D^{20}$ -10° (c 0.27, $CHCl_3$). IR ($CDCl_3$) 3475, 1753 sh, 1733 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, chloroform standard) δ 7.52-7.70 (m, 4H), 7.23-7.44 (m, 11H), 5.56 (dd, J= 2.9, 9.5 Hz, 1H), 5.37-5.52 (m, 1H), 5.10 (ABq, J= 18.4 Hz (calcd), 2H), 4.85 (dq, J= 2.7 , 6.4 Hz, 1H), 4.28-4.47 (m, 1H), 4.11 (dd, J= 1.4, 9.7 Hz, 1H), 3.12-3.25 (m, 1H), 2.27 (d, J= 5.9 Hz, 2H), 1.98-2.20 (m, 1H), 1.63-1.90 (m, 2H), 1.28 (d, J= 6.4 Hz, 3H), 1.15-1.37 (m, ~4H), 1.14 (d, J= 6.2 Hz, 3H), 0.98 (d, J=6.5 Hz, 6H), 0.76-0.90 (m, ~3H), 0.69 (s, 9H), -0.02 (s, 3H), -0.07 (s, 3H). MS (20eV), m/z (relative %) 798 (M^+, <1), 741 (3.4), 640 (4.8), 4.33 (29.7), 432 (100.0, base), 348 (12.3), 331 (13.8), 330 (56.0), 159 (16.3).

HRMS calcd for $C_{46}H_{62}N_2O_8Si$ 798.4275, found 798.4238.

(+)-(1R, 2R, 3S)-2-(3-N-Benzyloxy carbonyl-L-threonyloxy)-1-n-butyl-2-isobutylcarbonyloxybutyl)-4,5-diphenyloxazole **17**. To a solution of oxazole **16** (981 mg, 1.23 mmol) in 8 mL of THF at 0 °C was added via syringe a 0.82 M solution of tetra-n-butylammonium fluoride in THF (Aldrich Chem. Co., 3.00 mL, 2.46 mmol, 2.00 equiv) over 15 min. After it was stirred at 0 °C for an additional 25 min, the reaction mixture was diluted with 175 mL of Et_2O and washed with 150 mL of water. The aqueous layer was extracted with 150 mL of Et_2O, and the combined Et_2O extracts were dried over $MgSO_4$, and evaporated *in vacuo* to give a crude yellow oil. Flash chromatography (gradient elution with 85:15 to 7:3 pentane:Et_2O) gave 539 mg (64%) of **17** (R_f 0.64, 1:2 pentane:Et_2O) as a colorless glass. The material exhibited marked foaming tendencies, such that it required preliminary evaporation of solvent by nitrogen stream, followed by further evaporation under high vacuum at

~40°C. $[\alpha]_D^{21}$ + 6.0° (c 0.92, $CHCl_3$) IR ($CDCl_3$) 3725, 3475, 1752 sh, 1737 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ (7.52-7.70 (m, 4H), 7.23-7.45 (m, 11H), 5.62 (d, J= 9.6 Hz, 1H), 5.54 (dd, J= 3.5, 8.6 Hz, 1H), 5.12 (s, 2H), 4.95 (dq, J= 3.5, 6.6 Hz, 1H), 4.17-4.40 (m, 2H), 3.65 (d, J= 4.7 Hz, 1H), 3.14-3.30 (m, 1H), 2.33 (d, J= 7.0 Hz, 2H), 1.97-2.30 (m, 1H), 1.65-1.93 (m, 2H), 1.10-1.42 (m, ~4H), 1.28 (d, J= 6.7 Hz, 3H), 1.20 (d, J= 6.4 Hz, 3H), 1.01 (d, J= 6.5 Hz, 6H), 0.86 (t, J= 6.7 Hz, 3H). MS (20 eV), m/z (relative %) 684 (M^+, 1.0), 474 (14.6), 431 (13.5), 348 (15.6), 347 (48.5), 346 (100.0, base), 331 (23.3), 330 (74.6), 304 (11.9), 291 (10.2).

HRMS calcd for $C_{40}N_{48}N_2O_8$ 684.3410, found 684.3418.

(+)-(3S, 4R, 7R, 8R, 9S)-3-Benzyloxycarbonylamino-7-n-butyl-4,9-dimethyl-1,5-dioxa-8-isobutylcarbonyloxycyclononane-2,6-dione) **6**. A solution of hydroxyoxazole **17** (278 mg, 0.406 mmol) in 10 mL of CH_2Cl_2 was oxygenated in the presence of Sensitox (Rose Bengal polymer, 20 mg) during irradiation with a tungsten-halogen light source (650 w) operating at 85V for 3 h. The crude reaction mixture was filtered directly into 10.00 mL of xylenes, then the CH_2Cl_2 was removed under reduced pressure. The xylenes solution of triamide **18** (not isolated) was added via mechanically-driven syringe to a refluxing mixture of pyridinium p-toluenesulfonate (20 mg) in 90 mL of xylenes over 6 h. After cooling to room temperature, the reaction mixture was washed with 80 mL of cold saturated $NaHCO_3$ (aq), then the xylenes extract was dried over Na_2SO_4 and evaporated under high vacuum (bath temperature ~40 °C) to produce a crude yellow oil-solid mixture. Flash chromatograpy (gradient elution with 95:5 to 7:3 pentane:Et_2O) provided 40 mg (20%) of the title compound (R_f 0.43, 2:1 pentane:Et_2O) as a white crystalline solid. Recrystallization from Et_2O/pentane gave an analytical sample as white, feathery needles which exhibited physical and spectroscopic properties quite comparable to those reported in the literature.[7,3] mp 106.5-108.5 °C [lit, mp 109.0-109.5°C]. $[\alpha]_D^{22}$ + 56.1° (c 1.36, $CHCl_3$) [lit, $[\alpha]_D^{22}$ + 55° (c 1.24, $CHCl_3$)]. FTIR (CCl_4) 3440, 3436, 1754, 1733 cm^{-1} [lit, IR (CCl_4) 3440, 1756, 1738 cm^{-1}]. A 100 MHz ^1H NMR spectrum was completely superimposable on a 100 MHz spectrum of the authentic material indepedently prepared and kindly made available to us by M. Kinoshita. MS (20 eV), m/z (relative %) 491 (M^+, 0.6), 347 (36.5), 257 (23.2), 245 (10.6), 155 (23.7), 91 (100.0, base), 85 (19.5).

HRMS calcd for $C_{26}H_{37}NO_8$ 491.2519, found 491.2501.

Further elution provided 14 mg (7%) of a second dilactone component **6a** (R_f 0.31, 2:1 pentane:Et_2O) as a thick, colorless oil. By comparison with a similar by-product in other studies,[7] the structure may be assigned tentatively as the C-7 epimer. IR ($CDCl_3$) 3475, 1752, 1742, 1734, 1727 sh cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$), δ 7.36 (br s, 5H), 5.46-5.60 (m, 2H), 5.19-5.32 (m, 1H), 5.12 (s, 2H), 5.04 (dd, J= 3.8, 7.2 Hz, 1H), 4.86-4.98 (m, 1H), 2.83 (dt, J= 4.1, 10.3 Hz, 1H), 2.21 (d, J= 6.4 Hz, 2H), 2.03-2.20 (m, 1H), 1.54-1.74 (m, 2H), 1.13-1.52 (m, ~4H), 1.30 (d, J= 6.4 Hz, 3H), 1.27 (d, J= 7.6 Hz, 3H), 0.96 (d, J= 6.4 Hz, 6H), 0.86 (t, J= 6.9 Hz, 3H), 1.27 (d, J= 7.6 Hz, 3H), 0.96 (d, J= 6.4 Hz, 6H), 0.86 (t, J= 6.9 Hz, 3H). MS (20 eV), m/z (relative %) 491 (M^+, 0.5), 348 (28.4), 347 (100.0, base), 258 (12.9), 257 (75.0), 92 (11.5), 91 (98.4), 85 (16.2).

The ^1H NMR spectrum of **6a** is quite similar to that of **6** in most respects, but differs in the chemical shifts and patterns of the m, δ 5.19-5.23 and dt, 2.83 which are present in the natural isomer **6** at δ 4.75-5.10 and 2.46 respectively.

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