HETEROCYCLES, Vol. 75, No. 6, 2008, pp. 1385 - 1396. © The Japan Institute of Heterocyclic Chemistry
Received, 22nd December, 2007, Accepted, 25th February, 2008, Published online, 26th February, 2008. COM-07-11313

A FACILE SYNTHESIS OF CYCLOETHER SYSTEMS BEARING [2,4]-OXAZOLE UNITS

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Abstract – We present a concise and high-yielding route for the preparation of novel five-, six-, and seven-membered cycloether systems bearing [2,4]-oxazoles units. The approach is based on intramolecular electrophilic oxirane ring expansion strategies and β-hydroxyamide cyclodehydration-oxidation reactions mediated by Deoxo-Fluor and $BrCCl_3$/DBU.

INTRODUCTION

Cycloethers bearing 2,4-substituted oxazole moieties are present in a wide range of biologically active natural products. Such is the case of the C15-C32 fragment of the phorboxazoles, unique macrolides isolated from Indian Ocean sponges from the *Phorbas* sp. (**1** and **2**, Figure 1).[1] In addition to antifungal properties, both epimers possess exceptional cytostatic activity throughout the National Cancer Institute (NCI) panel of sixty human tumor cell lines, with an average IG_{50} below 0.8 nM. Recent studies with fluorescent phorboxazole derivatives indicate that these molecules induce association between extranuclear cytokeratin intermediate filaments (KRT10) and cyclin-dependent kinase 4 (CDK4), leading to a disruption of the cellular cycle at the G1-S interphase.[2] The ability of these molecules to halt cell division at this stage not only gives them enormous potential as antineoplastic agents, but could also complement and enhance the activity of drugs that cause arrest between the G2 and M phases (e.g. discodermolide, paclitaxel, and the epothilones).[2,3] In addition to their remarkable antitumor activity and novel mechanism of action, the phorboxazoles display a number of unprecedented structural features

which have inspired widespread interest among the synthetic community and have led to nine published total syntheses to date.[4]

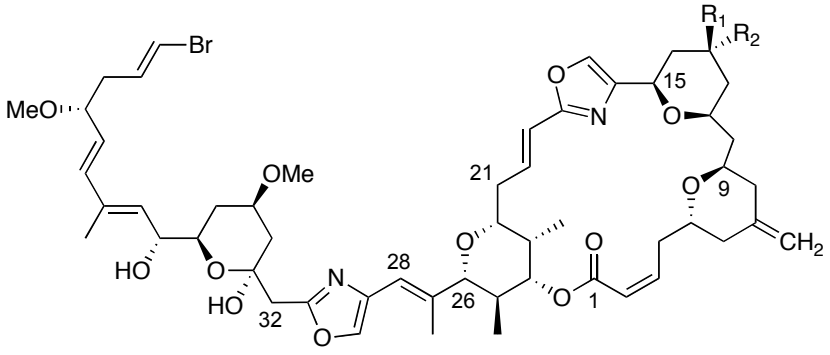


Figure 1. Structure and numbering of phorboxazole A (**1**, R_1 = H, R_2 = OH) and B (**2**, R_1 = OH, R_2 = H).

Recent studies on a series of phorboxazole analogs have led to the development of the minimal pharmacohore necessary for potent anticancer activity. These efforts revealed that a virtually intact macrolide ring, the central oxazole group, and the polyene side chain are essential for high activity,[5] and should be present or mimicked in simplified bioactive analogs. Therefore, the synthesis of phorboxazole analogs requires of straightforward strategies for the preparation of these fragments and their derivatives. In this letter, we describe a concise and high-yielding synthesis of novel five-, six-, or seven-membered oxanes bearing 2,4-substituted oxazole side chains. These compounds represent simplifications of the C15-C32 fragment of the phorboxazoles, and have the general structure shown in Figure 2.

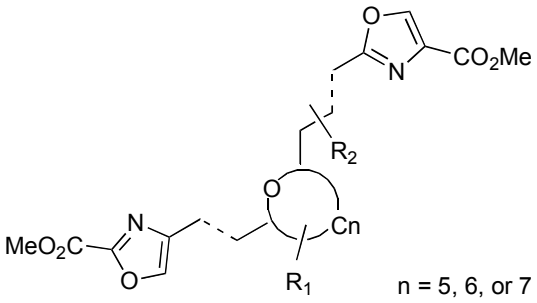
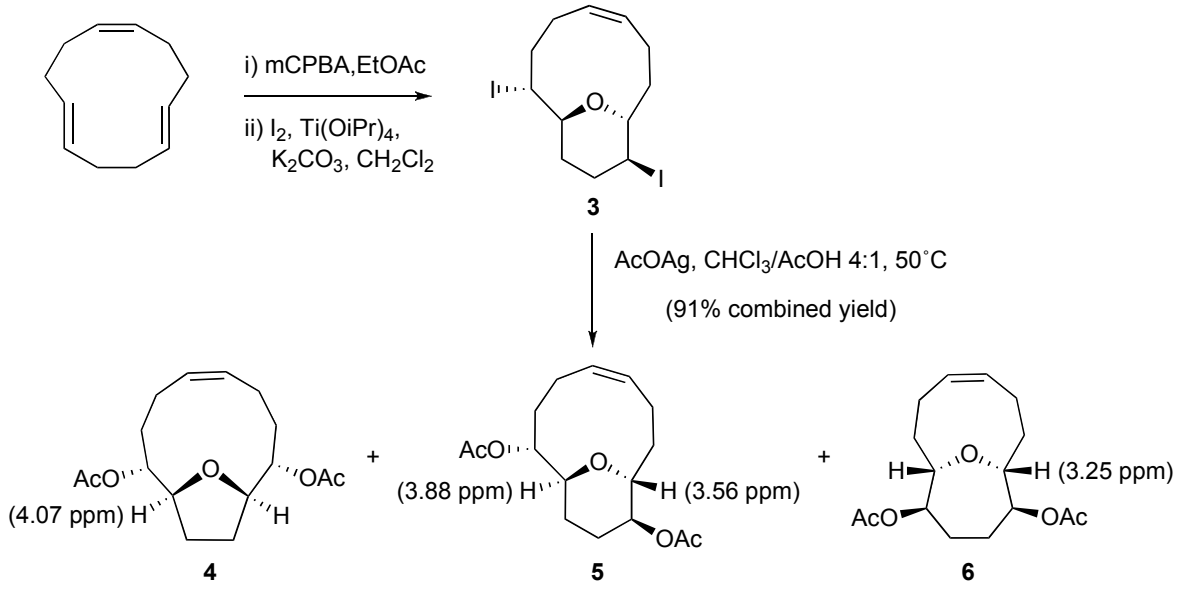


Figure 2. General structure of simplified analogs of the C15-C32 fragment of the phorboxazoles.

RESULTS AND DISCUSSION

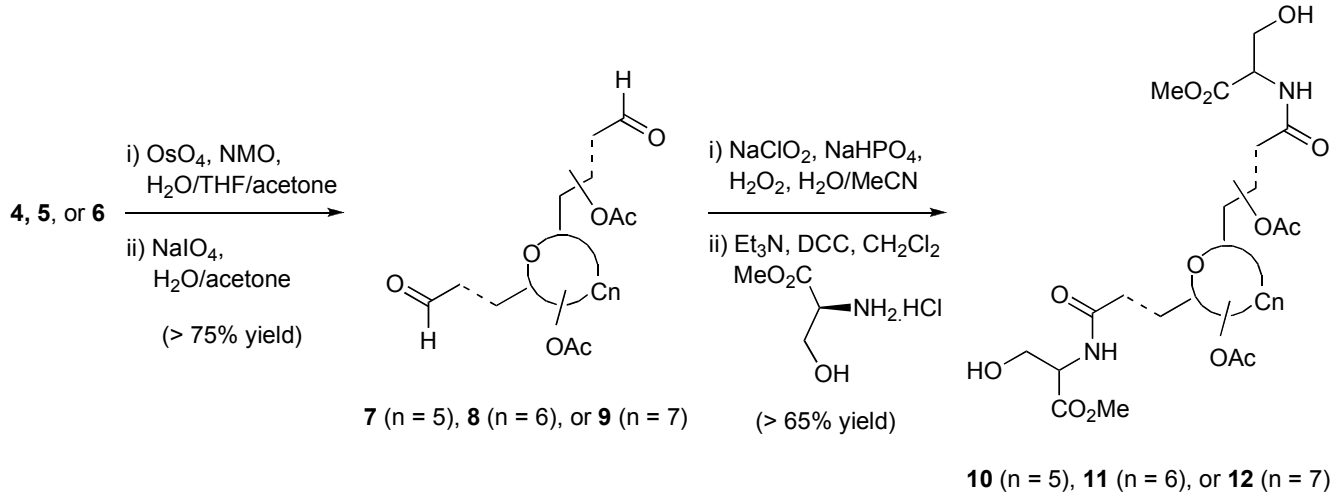
Our synthetic strategy is based on starting materials available through electrophilic intramolecular oxirane ring expansions of cyclic *cis*-epoxy alkenes, a methodology developed previously in our laboratories and applied successfully to the preparation of a variety of cycloethers.[6,7] Following this approach leads to

diiodooxabicycle **3**, a compound that contains all the required functionality and four chiral centers with defined relative stereochemistry.[7]



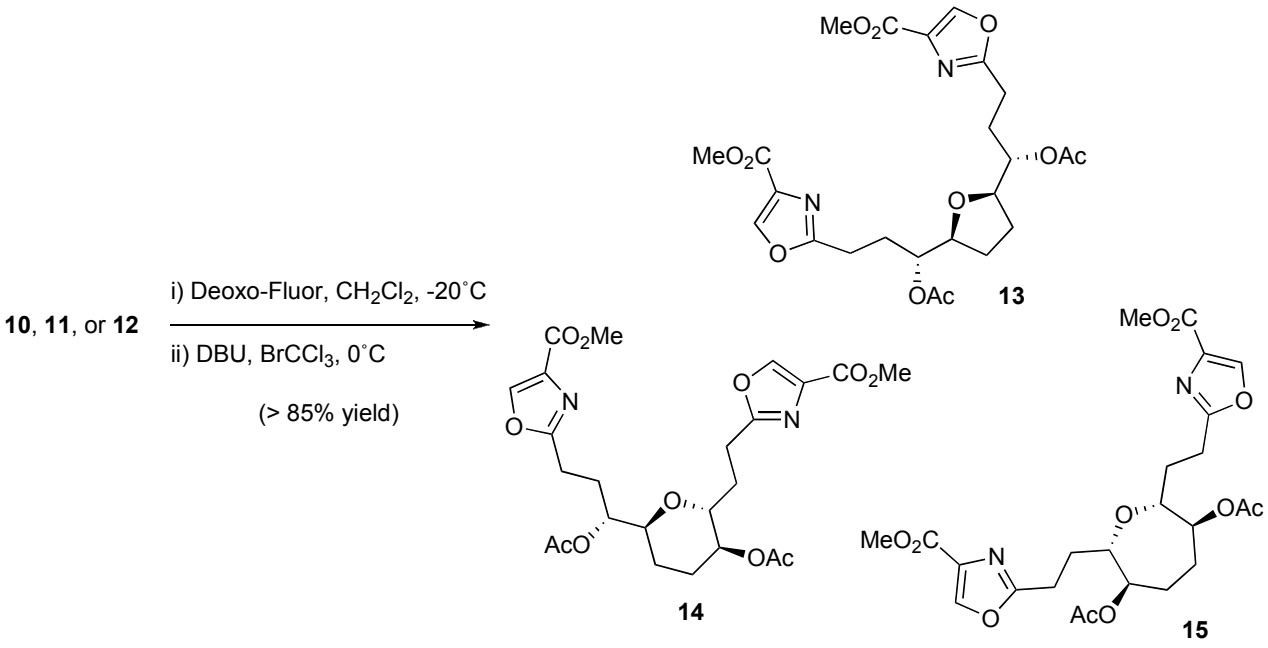
Scheme 1. Synthesis of diacetates **4**, **5**, and **6**. The oxane protons employed in the calculation of the product ratio and their chemical shifts are indicated.

As detailed in Scheme 1, solvolysis of **3** affords diacetates **4**, **5**, and **6**, in an approximate ratio of 5:8:4 as determined by integration of the oxane ^{1}H NMR signals. These compounds are obtained in agreement with the expected chemo-, regio-, and stereoselectivity, corroborating that the reaction occurs exclusively under conformational control induced by the cyclododecatriene system.



Scheme 2. Synthesis of bis-β-hydroxiamides **10**, **11**, and **12**.

cis-Dihydroxylation of **4**, **5**, and **6** with OsO_4 leads to a 3:1 mixture of α/β vicinal diols in approximately 95% combined yield.[8] Subsequent fragmentation of these diols with $NaIO_4$ affords dialdehydes **7**, **8**, and **9** in good yields.[9] These are then oxidized with $NaClO_2/H_2O_2$ to the corresponding diacids,[10] which are then condensed with L-serine methyl ester under standard amidation conditions to give bis-β-hydroxyamides **10**, **11**, and **12** (Scheme 2). It is worth noting that these three compounds were obtained as diastereomeric mixtures that do not need to be resolved prior to the next reaction step.



Scheme 3. Synthesis of bis-oxazoles oxanes **13**, **14**, and **15**.

The conversion of bis-β-hydroxyamides **10**, **11**, and **12** into the corresponding bis-oxazoles can be carried out by means of a cyclodehydration-oxidation.[11] Different reagents and conditions were explored to achieve this transformation, including dehydrating methods involving $SOCl_2$ followed by basic media,[12] use of PEG-supported Burgess reagent,[13] Mitsunobu conditions,[14] and oxidation with activated MnO_2.[15] None of these methods gave satisfactory results, and in all cases mixtures of bis-oxazoles, bis-oxazolines, and bis-acrylates in varying ratios were obtained. On the other hand, treatment of bis-β-hydroxyamides **10**, **11** and **12** with Deoxo-Fluor followed by $BrCCl_3$/DBU according to the methodology of Phillips and coworkers led exclusively to the desired bis-oxazoles in good yields (Scheme 3).[16] The success of the reactions was initially confirmed by the presence of signals at approximately 8.1 ppm in the ^1H NMR spectra of the purified products, and which correspond to the 5-position protons of the oxazole moieties (see below). The new compounds were then thoroughly characterized using 1D- and 2D-NMR spectroscopic techniques.[17]

In conclusion, this communication described the preparation of a new class of oxanes bearing [2,4]-oxazole substituents in good yields and from readily available precursors. The synthetic route further showcases the electrophilic intramolecular oxirane ring expansion approach for the stereoselective synthesis of five-, six-, and seven-membered cycloethers, as well as the use of Deoxo-Fluor and $BrCCl_3$/DBU in the preparation of [2,4]-substituted oxazoles. The biological activity of these novel compounds is being assessed, and the results from these investigations will be reported in due course.

EXPERIMENTAL

General

Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. Flash column chromatography was carried out using 230-400 mesh silica gel. IR spectra were recorded on a Shimadzu 8101 FT-IR spectrophotometer. NMR experiments were carried out on a Bruker AVANCE 400 spectrometer operating at ^1H and ^{13}C frequencies of 400.13 and 100.61 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual $CDCl_3$ signal (7.28 ppm), and couplings constants (*J*) are given in Hertz. MS and HRMS spectra were recorded on Shimadzu GC-MS QP 1100 EX and VG AutoSpec Q mass spectrometers, respectively, using in both cases electron-impact ionization. Elemental analyses were performed on a Fisions EA 1108 CHNS-O microanalyzer.

(1*R,8*R**,9*S**,12*S**,*Z*)-8,12-Diiodo-13-oxabiciclo[7.3.1]tridec-4-ene (3)**. (1*E*,5*E*,9*Z*)-cyclododecatriene (64.8 g, 0.4 mol) in EtOAc (80 mL) was treated with a solution of mCPBA (70.6 g, 0.4 mol) in EtOAc (250 mL) so as to keep the reaction temperature below 10 ºC. The mixture was then stirred for 2 h at room temperature, and extracted with a 10 % aqueous $Na_2S_2O_3$ (3 × 80 mL), 3M NaOH (3 × 70 mL), and H_2O (3 × 70 mL). The organic layer was dried over $MgSO_4$, the solvent evaporated under reduced pressure, and the crude product purified by column chromatography (*n*-hexane/EtOAc 9:1). This material (38 g, 0.21 mol) was subsequently diluted in CH_2Cl_2 (380 mL), and added slowly to previously prepared slurry of crushed molecular sieves (38 g), K_2CO_3 (46 g, 0.32 mol), I_2 (27 g, 0.11 mol), and $Ti(OiPr)_4$ (47.3 mL, 0.16 moles) in CH_2Cl_2 (1000 mL). The reaction mixture was then diluted with Et_2O (250 mL), and the organic layer washed with 15% aqueous $Na_2S_2O_3$ (3 × 100 mL), saturated $NaHCO_3$ (3 × 100 mL), brine (3 × 100 mL), and dried with $MgSO_4$. The solvent was removed under vacuum to yield a 3:1 mixture of [8.2.1] and [7.3.1] diiodooxabicycles. Column chromatography of this mixture (hexanes/EtOAc 98:2) gave **3** in 22% overall yield (21.5 g). Crystalline solid, mp 125-127 ºC, R_f = 0.25 (*n*-hexane). IR (film): 3433, 2999, 2964, 2923, 2885, 2849, 1445, 1434, 1380, 1372, 1346, 1337, 1232, 1219, 1151, 1136, 1090, 1050, 1013, 998, 863, 846, 717, 702, 686 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.54 (m,

2H), 4.68 (ddd, *J* = 12.2, *J* = 10.8, *J* = 3.6, 1H), 4.16 (m, 1H), 3.98 (ddd, J = 10.4, *J* = 9.9, *J* = 4.2), 3.74 (ddd, *J* = 11.1, *J* = 10.4, *J* = 3.2, 1H), 3.03 (dddd, *J* = 13.8, *J* = 13.7, *J* = 11.2, *J* = 3.9, 1H), 2.69 (dddd, *J* = 13.8, *J* = 13.7, *J* = 4.8, *J* = 3.6, 1H), 2.60 (dddd, *J* = 12.9, *J* = 12.9, *J* = 10.8, *J* = 5.3, 1H), 2.46 (dddd, *J* = 13.8, *J* = 12.2, *J* = 3.9, *J* = 3.7, 1H), 2.27 (m, 2H), 2.19 (m, 3H), 1.87 (m, 1H), 1.79 (m, 1H), 1.42 (dddd, *J* = 13.6, *J* = 11.1, *J* = 5.3, *J* = 2.2, 1H). ^{13}C NMR ($CDCl_3$): δ 131.1, 128.8, 79.7, 73.6, 44.7, 35.6 (2), 33.8 (2), 32.4, 31.4, 30.7, 29.3, 22.8. MS: *m/z* (rel. int.) 432 (0.5, $[M]^+$), 305 (25, $[M - I]^+$), 159 (33), 133 (12), 117 (14), 107 (22), 93 (34), 79 (63), 67 (100), 55 (61), 41 (70).

Preparation of compounds 4, 5, and 6

To a stirred solution of diiodooxabicycle **3** (300 mg, 0.69 mmol) in dry $CHCl_3$ (5 mL) were added AgOAc (315 mg, 1.9 mmol) and AcOH (1.2 mL). The mixture was refluxed for 24 h, the solvent was partially removed under vacuum, and the residue was diluted with Et_2O (10 mL). The resulting solution was washed with saturated aqueous $NaHCO_3$ (3 × 10 mL), H_2O (2 × 10 mL), and brine (10 mL), dried with $MgSO_4$, and the solvent removed under reduced pressure. The crude material was purified in two stages by flash column chromatography (EtOAc/*n*-hexane 1:3 – $CHCl_3$) to afford diacetates **6**, **4**, and **5** in 91% combined yield (175 mg). The relative ratios of **4** (29%), **5** (47%), and **6** (24%) were determined from the ^{1}H NMR spectrum of the original mixture.

(1*R,2*S**,9*R**,10*S**,*Z*)-13-Oxabicyclo[8.2.1]tridec-5-ene-2,9-diyl diacetate (4)**. Obtained as a crystalline solid, mp 115-117 ºC, R_f = 0.52 (EtOAc/*n*-hexane 3:7). IR (film): 3026, 3009, 1731, 1444, 1374, 1250, 1187, 1119, 1029, 975, 904, 778, 768, 755, 736, 720 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.49 (m, 2H), 4.62 (ddd, *J* = 11.1, *J* = 9.4, *J* = 3.1, 2H), 4.07 (m, 2H), 2.88 (m, 2H), 2.03 (s, 6H), 1.90 (m, 4H), 1.75 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 170.1, 130.0, 83.5, 74.1, 33.8, 29.3, 23.5, 21.6. MS: *m/z* (rel. int.) 296 (3, $[M]^+$), 253 (20), 236 (52), 210 (24), 194 (25), 176 (100), 158 (16), 150 (22), 143 (7), 137 (11), 132 (38), 119 (32), 113 (23), 106 (66), 97 (45), 93 (39), 83 (22), 79 (63), 71 (21), 67 (69), 54 (40). HRMS: *m/z* calcd for $C_{16}H_{24}O_5$ 296.1624 ($[M]^+$), found 296.1633.

(1*S,2*R**,9*R**,10*S**,*Z*)-13-Oxabicyclo[7.3.1]tridec-5-ene-2,10-diyl diacetate (5)**. Obtained as a crystalline solid, mp 75-77 ºC, R_f = 0.58 (EtOAc /*n*-hexane 3:7). IR (film): 3026, 3009, 2924, 1731, 1444, 1374, 1250, 1187, 1119, 1029, 975, 904, 778, 768, 755, 736, 720 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.61 (ddd, *J* = 13.1, *J* = 11.6, *J* = 3.6, 1H), 5.41 (dddd, *J* = 11.9, *J* = 11.6, *J* = 5.4, *J* = 1.5, 1H), 5.30 (ddd, *J* = 10.7, *J* = 10.4, *J* = 3.9, 1H), 4.54 (ddd, *J* = 9.8, *J* = 9.6, *J* = 4.8, 1H), 3.88 (ddd, *J* = 10.4, *J* = 6.0, *J* = 2.3, 1H), 3.56 (ddd, *J* = 12.1, *J* = 9.8, *J* = 3.2, 1H), 2.98 (dddd, *J* = 13.5, *J* = 13.5, *J* = 13.1, *J* = 3.9, 1H), 2.56 (dddd, *J* = 12.6, *J* = 12.6, *J* = 12.3, *J* = 5.3, 1H), 2.04 (s, 3H), 2.01 (s, 3H), 1.93 (m, 5H), 1.75 (m, 2H), 1.57 (m, 2H),

1.42 (dddd, J = 13.6, J = 12.1, J = 5.3, J = 2.2, 1H). ^{13}C NMR ($CDCl_3$) δ: 170.7, 170.3, 131.9, 128.2, 76.3, 72.7, 71.1, 67.1, 35.4, 28.5, 26.5, 24.9, 23.8, 22.2, 21.6, 21.5. MS: *m/z* (rel. int.) 296 (26, $[M]^+$), 254 (9), 236 (39), 210 (9), 194 (33), 176 (100), 158 (11), 150 (32), 143 (6), 137 (14), 132 (27), 126 (10), 119 (19), 113 (16), 106 (43), 97 (41), 93 (38), 84 (51), 79 (53), 71 (12), 67 (62), 54 (31). HRMS: *m/z* calcd for $C_{16}H_{24}O_5$ 296.1624 ($[M^+]$), found 296.1627.

(1*S,8*R**,9*S**,12*R**,*Z*)-13-Oxabicyclo[6.4.1]tridec-4-ene-9,12-diyl diacetate (6)**. Obtained as a crystalline solid, mp 135-137 ºC, R_f = 0.58 (EtOAc/*n*-hexane 3:7). IR (film): 3026, 3009, 2924, 1731, 1444, 1374, 1250, 1187, 1119, 1029, 975, 904, 778, 768, 755, 736, 720 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.60 (m, 2H), 4.75 (m, 2H), 3.25 (ddd, J = 11.4, J = 9.1, J = 4.6, 2H), 2.77 (m, 2H), 2.03 (s, 6H), 1.92 (m, 4H), 1.86 (m, 4H), 1.68 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 170.6, 130.5, 85.6, 77.4, 31.9, 26.1, 22.4, 21.6. MS *m/z* (rel. int.): 296 ($[M]^+$, 26), 254 (9), 210 (9), 194 (33), 176 (100), 158 (11), 150 (32), 143 (6), 137 (14), 132 (27), 126 (10), 119 (19), 113 (16), 106 (43), 97 (41), 93 (38), 84 (51), 79 (53), 71 (12), 67 (62), 54 (31). HRMS: *m/z* calcd for $C_{16}H_{24}O_5$ 296.1624 ($[M^+]$), found 296.1631.

Preparation of compounds 7, 8, and 9

To a stirred mixture of 4-methylmorpholine *N*-oxide (1.214 g, 8.98 mmol) and water (0.8 mL) at 25 ºC was added OsO_4 (0.254 mg, 0014 mmol), followed by a solution of compound **4** (78 mg, 0.264 mmol) in THF/acetone (1:1, 1.6 mL). After 12 h at 25 ºC the reaction mixture was treated with a saturated aqueous solution of Na_2SO_3 (0.4 mL) and diluted with EtOAc (15 mL). The organic layer was washed with H_2O (2 × 10 mL), brine (10 mL), and dried over $MgSO_4$. Concentration followed by flash chromatography (EtOAc/*n*-hexane 1:1) afforded a 3:1 mixture of diastereomeric diols. These were subsequently dissolved in acetone/H_2O (4:1, 5.0 mL) and treated with $NaIO_4$ (97.3 mg, 0.3 mmol) at 25ºC under an argon atmosphere. The resulting reaction mixture was stirred for 15 h, diluted with Et_2O (10 mL), and washed with H_2O (2 × 7 mL). The aqueous layers were combined and extracted with Et_2O (3 × 20 mL). The combined organic layers were then dried with $MgSO_4$, and the solvent removed under reduced pressure. The crude product was then purified chromatographically (EtOAc/*n*-hexane 10:3) to give compound **7** in 79% for the two steps (68 mg). An analogous procedure was used to convert compounds **5** and **6** into dialdehydes **8** and **9**.

(2*S,5*R**)-2-((*R**)-1-Acetoxy-4-oxobutyl)-5-((*S**)-1-acetoxy-4-oxobutyl)tetrahydrofuran (7)**. Obtained as a colorless oil, R_f = 0.45 (*n*-hexanes/EtOAc, 3:7), IR (film): 2820.9, 2755.3, 1732.1, 1462.2, 1373.5, 1240.4, 1132.4, 1078.3, 1030.1, 954.9, 883.5, 667.5 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.77 (t, J = 1.3, 2H), 4.91, (ddd, J = 9.1, J = 5.7, J = 3.7, 2H), 3.94 (m, 2H), 2.51 (m, 4H), 2.08 (s, 6H), 2.06 (m, 2H),

1.89 (m, 4H), 1.76 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 201.5, 170.9, 80.7, 74.3, 40.2, 27.5, 23.8, 21.4. MS: *m/z* (rel. int.) 329 (2, $[M]^+$), 269 (7), 225 (30), 209 (30), 199 (100), 191 (24), 139 (50), 99 (34), 71 (75), 61 (75). HRMS: *m/z* calcd for $C_{16}H_{24}O_7$ ($[M]^+$) 329.1600, found 329.1583.

(2*R,3*S**,6*S**)-3-Acetoxy-6-((*R**)-1-acetoxy-4-oxobutyl)-2-(3-oxopropyl)tetrahydro-2*H*-pyran (8)**. Obtained as a colorless oil, R_f = 0.50 (*n*-hexanes/EtOAc, 3:7). IR (film): 2835, 1716, 1437, 1373, 1238, 1115, 1032, 968, 893, 826, 758, 667 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.81 (t, *J* = 1.3, 1H), 9.78 (t, *J* = 1.3, 1H), 5.05 (ddd, *J* = 9.7, *J* = 7.2, *J* = 3.0, 1H), 4.62 (ddd, *J* = 5.5, *J* = 4.3, *J* = 4.3, 1H), 3.74 (ddd, *J* = 9.6, *J* = 4.3, *J* = 4.3, 1H), 3.60 (ddd, *J* = 7.6, *J* = 7.2, *J* = 3.8, 1H), 2.59 (m, 2H), 2.51 (m, 2H), 2.17 (m, 1H), 2.09 (s, 3H), 2.05 (s, 3H), 1.94 (m, 1H), 1.85 (m, 4H), 1.63 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 201.7, 201.6, 170.9, 170.8, 74.4, 72.9, 71.3, 70.5, 40.3, 40.0, 24.0, 23.3, 23.0, 22.9, 21.6(2), 21.3(2). MS: *m/z* (rel. int.) 345 (0.8, $[M]^+$), 240 (18), 222 (18), 215 (57), 194 (8), 181 (6), 167 (9), 155 (63), 138 (61), 137 (33), 111 (21), 96 (16), 85 (30), 81 (16), 60 (12), 43 (100). HRMS: *m/z* calcd for $C_{16}H_{26}O_7$ ($[M]^+$) 329.1600, found 329.1412.

(2*R,3*S**,6*R**,7*S**)-3,6-Diacetoxy-2,7-bis(3-oxopropyl)oxepane (9)**. Obtained as a colorless oil, R_f = 0.5 (*n*-hexanes/EtOAc, 3:7). IR (film): 2874, 2135, 1700, 1456, 1219, 1030, 903, 772, 667 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 9.82 (t, *J* = 1.3, 2H), 4.73 (m, 2H), 3.47 (ddd, *J* = 8.6, *J* = 7.4, *J* = 3.5, 2H), 2.54 (m, 4H), 2.08 (s, 6H), 1.94 (m, 4H), 1.86 (m, 2H), 1.73 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 202.1, 170.4, 82.5, 75.8, 40.2, 26.6, 25.7, 21.6. MS: *m/z* (rel. int.) 329 (5, $[M]^+$), 269 (15), 225 (36), 209 (100), 191 (77), 141 (70), 139 (65), 122 (60), 99 (78), 71 (100), 61 (52). HRMS: *m/z* calcd for $C_{16}H_{24}O_7$ ($[M]^+$) 329.1600, found 329.1593.

Preparation of compounds 10, 11, and 12

A solution of $NaClO_2$ (928 mg, 8.12 mmol, 79% purity by iodometric titration) in water (10 mL) was added dropwise over a 2 h period to a stirred mixture of dialdehyde **7** (940 mg, 2.9 mmol), acetonitrile (5 mL), 35% H_2O_2 (560 μL), and NaH_2PO_4 (180 mg) in water (2.5 mL), keeping the temperature at 10 ºC. Oxygen evolving from the solution was monitored with a bubbler connected to the apparatus until the end of the reaction (about 2 h). A small amount (~ 0.5 g) of Na_2SO_3 was then added to destroy the unreacted HOCl and H_2O_2, the mixture was acidified with 10% HCl, and extracted with CH_2Cl_2. The organic layers were dried with $MgSO_4$, and the solvent removed under vacuum. The resulting crude diacid, together with L-serine methyl ester hydrochloride (0.93 g, 6.0 mmol), 1-hydroxybenzotriazole monohydrate (0.81 g, 6.0 mmol), and Et_3N (1.21 g, 12.0 mmol) were dissolved in dry CH_2Cl_2 (25 mL), cooled to ºC, and treated with DCC (1.86 g, 9.0 mmol) under constant stirring. The reaction mixture was held at 0 ºC for 1 h,

followed by 1 h at rt. The precipitated DCU was then removed by filtration, and the solvent evaporated *in vacuo*. Flash column chromatography (MeOH/EtOAc 1:10) provided bis-amide **10** as a diastereomeric mixture in 66% yield (1.06 g). Dialdehydes **8** and **9** were converted into bis-amides **11** and **12** following an identical protocol.

(2*S,5*R**)-2-((*R**)-1-Acetoxy-4-((*S*)-3-hydroxy-1-methoxy-1-oxopropan-2-ylamino)-4-oxobutyl)-5-((*S**)-1-acetoxy-4-((*S*)-3-hydroxy-1-methoxy-1-oxopropan-2-ylamino)-4-oxobutyl)tetrahydrofuran (10)**. Obtained as a yellow oil, R_f = 0.45 (MeOH/EtOAc 1:10). IR (film): 2953, 1736, 1655, 1516, 1437, 1375, 1240, 1148, 1113, 1074, 1032, 993, 895, 756, 667 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.04 (d, *J* = 7.6, 2H), 6.84 (d, *J* = 7.6, 2H), 4.83 (m, 4H), 4.63 (m, 4H), 3.92 (m, 12H), 3.76 (s, 12H), 2.34 (m, 6H), 2.24 (m, 2H), 2.15 (m, 2H), 2.08 (s, 6H), 2.06 (s, 6H), 2.03 (m, 2H), 1.92 (m, 6H), 1.77, (m, 2H), 1.70 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 173.4, 172.9, 171.9, 171.4 (2), 171.3, 81.0 (2), 75.0, 74.7, 63.2, 63.1, 55.3, 55.2, 53.0, 52.9, 32.7, 32.5, 28.0, 27.7, 27.6, 27.5, 21.6, 21.5. MS: *m/z* (rel. int.) 563 (2, $[M]^+$), 544 (10), 532 (68), 444 (36), 316 (100), 298 (30), 241 (25), 181 (28), 120 (88), 102 (42), 85 (30), 60 (80). HRMS: *m/z* calcd for $C_{24}H_{38}N_2O_{13}$ (M^+) 563.2452, found 563.2451.

(2*R,3*S**,6*S**)-3-Acetoxy-6-((*R**)-1-acetoxy-4-((*S*)-3-hydroxy-1-methoxy-1-oxopropan-2-ylamino)-4-oxobutyl)-2-(3-((*S*)-3-hydroxy-1-methoxy-1-oxopropan-2-ylamino)-3-oxopropyl)tetrahydro-2*H*-pyran (11)**. Obtained as a yellow oil, R_f = 0.5 (MeOH/EtOAc 1:10). IR (film): 3322, 2958, 2932, 2855, 1736, 1655, 1541, 1439, 1375, 1246,1144, 1044, 968 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.06 (d, *J* = 7.8, 1H), 7.02 (d, *J* = 7.8, 1H), 6.94 (d, *J* = 7.6, 1H), 6.81 (d, *J* = 7.6, 1H), 5.07 (m, 2H), 4.65 (m, 6H), 3.96 (m, 8H), 3.79 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.69 (m, 2H), 3.63 (m, 2H), 2.39 (m, 8H), 2.20 (m, 2H), 2.09 (s, 3H), 2.08 (s, 3H), 2.07 (s, 6H), 1.89 (m, 2H), 1.84 (m, 8H), 1.62 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 173.8, 173.4, 173.3, 173.1, 171.6 (3), 171.5, 171.4, 171.2. 171.1, 171.0, 74.4, 74.0, 73.2, 72.5, 71.2, 70.8, 70.7 (2), 63.4, 63.3, 63.2, 63.1, 55.2, 55.1 (3), 53.1 (2), 53.0 (2). 32.4, 32.3, 32.1, 32.0, 27.4, 27.3, 26.1, 25.7, 24.2, 24.1, 23.5, 22.8, 21.6 (2), 21.4 (2). MS: *m/z* (rel. int.): 563 (0.03, $[M]^+$), 532 (6), 444 (8), 384 (7), 298 (12), 186 (16), 120 (30), 60 (36), 43 (100). HRMS: *m/z* calcd for $C_{24}H_{38}N_2O_{13}$ ($[M]^+$) 563.2452, found 563.2450.

(2*R,3*S**,6*R**,7*S**)-3,6-Diacetoxy-2,7-bis(3-((*S*)-3-hydroxy-1-methoxy-1-oxopropan-2-ylamino)-3-oxopropyl)oxepane (12)**. Obtained as a yellow oil, R_f = 0.5 (MeOH/EtOAc 1:10). IR (film) ν_{max}: 2953, 1736, 1655, 1542, 1510, 1437, 1375, 1240, 1148, 1113, 1074, 1032, 993, 895, 756, 667 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.24 (d, *J* = 7.9, 2H), 7.21 (d, *J* = 7.9, 2H), 4.68 (m, 4H), 4.63 (m, 4H), 3.98 (m, 2H), 3.96 (m, 2H), 3.87 (m, 2H), 3.85 (m, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 3.56 (ddd, *J* = 9.6, *J* = 7.4, *J* = 2.5, 4H), 2.46

(m, 8H), 2.06 (s, 12H), 1.97 (m, 4H), 1.85 (m, 8H), 1.64 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 174.0, 173.9, 171.6, 171.5, 171.2, 170.8, 81.9, 81.7, 76.6, 76.0, 63.2, 63.1, 55.2, 55.1, 53.0 (2), 32.0, 31.8, 30.2, 29.7, 25.8, 25.5, 21.6 (2). MS *m/z* (rel. int.): 563 ([M]$^+$, 4), 544 (8), 532 (80), 503 (15), 444 (44), 384 (17), 316 (20), 300 (47), 214 (22), 186 (54), 120 (100), 60 (88). HRMS: *m/z* calcd for $C_{24}H_{38}N_2O_{13}$ ([M]$^+$) 563.2452, found 563.2460.

Preparation of compounds 13, 14, and 15

A solution of bis-β-hydroxyamide **10** (630 mg, 1.12 mmol) in CH_2Cl_2 was treated with Deoxo-Fluor (0.45 mL, 2.46 mmol) at -20 °C. After 30 min, DBU (2.20 mL, 14.7 mmol) was added dropwise to the reaction mixture at -20 ºC, followed by $BrCCl_3$ (1.44 mL, 14.7 mmol) at 0 ºC. The reaction was stirred at rt for 8 h, and then quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2, the combined organic layers were dried with $MgSO_4$, and the solvent removed under reduced pressure. Purification by flash chromatography (EtOAc) gave bis-oxazole **13** in 88% yield (540 mg). Bis-oxazoles **14** and **15** were obtained analogously from bis-amides **11** and **12**.

(2*S,5*R**)-2-((*R**)-1-Acetoxy-3-(4-(methoxycarbonyl)oxazol-2-yl)propyl)-5-((*S**)-1-acetoxy-3-(4-(methoxycarbonyl)oxazol-2-yl)propyl)tetrahydrofuran (13)**. Obtained as a colorless oil, R_f = 0.45 (EtOAc). IR (film): 3460, 2955, 2878, 1732, 1651, 1589, 1439, 1373, 1325, 1236, 1197, 1173, 1142, 1111, 1041, 951, 804, 772, 607, 544 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.14 (s, 2H), 4.93 (ddd, *J* = 9.0, *J* = 5.7, *J* = 3.6, 2H), 3.92 (m, 2H), 3.89 (s, 6H), 2.85 (ddd, *J* = 8.2, *J* = 6.8, *J* = 1.0, 4H), 2.14 (m, 2H), 2.03 (s, 6H), 2.01, (m, 2H), 1.90 (m, 2H), 1.73 (m, 2H).^{13}C NMR ($CDCl_3$): δ 170.8, 165.3, 162.0, 144.2, 133.6, 80.5, 74.1, 52.4, 28.4, 27.5, 24.6, 21.3. MS: *m/z* (rel. int.) 522 (0.04, [M]$^+$), 403 (4), 322 (13), 296 (100), 262 (33), 236 (30), 141 (33), 43 (94).

(2*R,3*S**,6*S**)-3-Acetoxy-6-((*R**)-1-acetoxy-3-(4-(methoxycarbonyl)oxazol-2-yl)propyl)-2-(2-(4-(methoxycarbonyl)oxazol-2-yl)ethyl)tetrahydro-2*H*-pyran (14)**. Obtained as a crystalline solid, mp: 90-92 ºC, R_f = 0.5 (EtOAc). IR (film): 3444, 2955, 2338, 1734, 1589, 1437, 1373, 1323, 1240, 1200, 1171, 1142, 1111, 1045, 1001, 772 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.16 (s, 2H), 5.05 (ddd, *J* = 9.0, *J* = 7.3, *J* = 2.9, 1H), 4.60 (ddd, *J* = 5.5, *J* = 3.8, *J* = 3.8, 1H), 3.90 (s, 6H), 3.78 (ddd, *J* = 9.9, *J* = 4.0, *J* = 4.0, 1H), 3.64 (ddd, *J* = 7.7, *J* = 7.7, *J* = 3.6, 1H), 2.94 (m, 1H), 2.86 (m, 2H), 2.29 (dddd, *J* = 14.5, *J* = 9.1, *J* = 7.3, *J* = 2.9, 1H), 2.11 (m, 2H), 2.08 (s, 3H), 2.05 (s, 3H), 1.86 (m, 3H), 1.63 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 170.8, 165.4, 165.3, 162.0, 144.2, 133.6, 74.2, 73.0, 71.1, 70.2, 52.5, 52.4, 27.9, 27.4, 24.5, 24.0, 22.8, 21.6, 21.3. MS: *m/z* (rel. int.) 522 (0.2, [M]$^+$), 402 (8), 322 (40), 296 (100), 262 (48), 236 (34), 141 (34), 43 (77). Anal. Calcd. for $C_{24}H_{30}N_2O_{11}$: C, 55.17; H, 5.79; N, 5.36. Found: C, 54.76; H, 5.96; N, 5.28.

(2*R,3*S**,6*R**,7*S**)-3,6-Diacetoxy-2,7-bis(2-(4-(methoxycarbonyl)oxazol-2-yl)ethyl)oxepane (15)**. Obtained as a crystalline solid, mp: 85-87 ºC, R_f = 0.5 (EtOAc). IR (film): 3447, 2993, 2992, 1736, 1588, 1439, 1373, 1325, 1236, 1200, 1140, 1111, 1032, 1003 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.15 (s, 2H), 4.72 (m, 2H), 3.90 (s, 6H), 3.51 (ddd, *J* = 9.0, *J* = 7.6, *J* = 3.2, 2H), 2.98 (ddd, *J* = 15.3, *J* = 9.3, *J* = 5.4, 2H), 2.90 (ddd, *J* = 15.3, *J* = 9.2, *J* = 6.9, 2H), 2.08 (m, 2H), 2.02 (s, 6H), 1.87 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 170.4, 165.5, 162.0, 144.1, 133.6, 82.4, 75.8, 52.4, 31.3, 25.7, 24.5, 21.6. MS: *m/z* (rel. int.) 522 (3, $[M]^+$), 463 (11), 403 (9), 322 (19), 296 (22), 280 (15), 262 (31), 236 (18), 180 (24), 141 (65), 43 (100). Anal. Calcd. for $C_{24}H_{30}N_2O_{11}$: C, 55.17; H, 5.79; , 5.36. Found: C, 54.51; H, 5.74; N, 5.25.

ACKNOWLEDGEMENTS

The authors wish to thank the Programa de Desarrollo de las Ciencias Básicas and the Fondo Clemente Estable (Grant FCE/2004/10050) for financial support (MI, CF, LS, and EM). GM acknowledges funding from the Camille and Henry Dreyfus Foundation (Award TH-08-004).

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