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ACTIVATED CARBOXYLATES FROM THE PHOTOOXYGENATION OF OXAZOLES

APPLICATION TO THE SYNTHESIS OF RECIFEIOLIDE, CURVULARIN AND OTHER MACROLIDES

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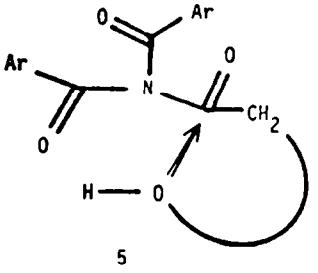
Abstract—Oxazoles may be used as masked forms of activated carboxylic acids since they readily form triamides on reaction with singlet oxygen. With 2-alkyl-4,5-diphenyloxazoles, the triamides formed on photooxygenation undergo selective nucleophilic attack at the acyl carbonyl derived from the 2-oxazole position. Using 2-(ω-hydroxyalkyl)-4,5-diphenyloxazoles as substrates, the oxidation–acylation sequence may be employed for the synthesis of macrolides including (±)-recifeiolide and (±)-di-O-methylcurvularin.

The formation of triamides from oxazoles by the action of singlet oxygen is a reaction which has many potential applications in organic synthesis. The conditions are mild, the yields are high, and the product, an activated form of a carboxylic acid, is a useful acylating agent.[1,2] Many examples of this transformation have now been reported, and mechanistic studies have elucidated the main features of this unusual oxidative process.[3,4]

As pictured in Scheme 1, the reaction appears to take place by formation of an unstable 2,5-endoperoxide (2) which undergoes rearrangement, most probably through an imino anhydride (3), to the triamide (4). Oxygen-18 studies[3] are in accord with a 2,5-endoperoxide rather than a 4,5-dioxetane pathway, and the isolation of a stable imino anhydride intermediate in the case of 2-aryl-4,5-polymethylene-oxazoles[4] supports the sequence pictured below.



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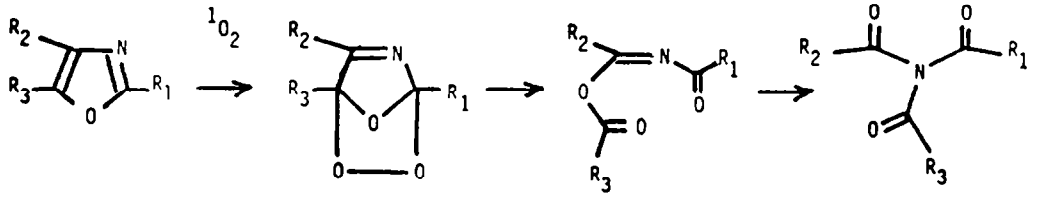
In this work we have made use of 2-alkyl-4,5-diphenyl-oxazoles as sources of latent carboxylic acid derivatives which can be readily "unmasked" by dye-sensitized photooxygenation. The oxazole group is an excellent carboxyl protecting group since it is relatively unreactive toward hydrolysis in both acid and base, is stable toward



1 2 3 4

Scheme 1.

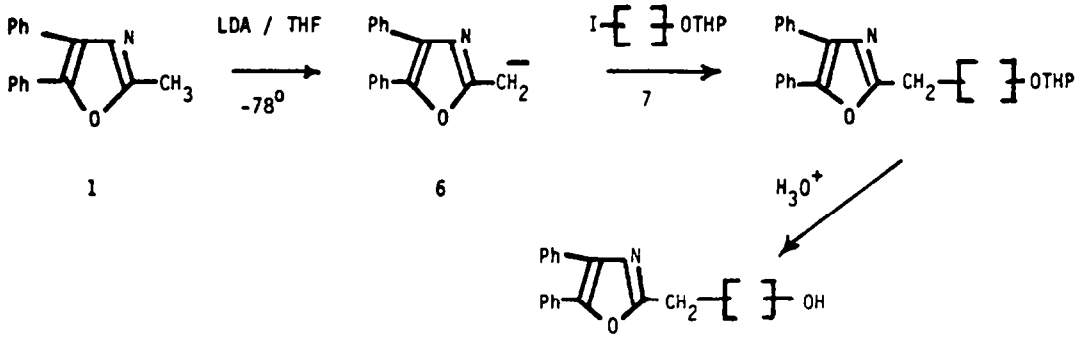
The formation of the triamides (4) in the above process effectively transforms all three C atoms of the oxazole to activated carboxylate derivatives. However, by proper choice of substituents, it is possible to limit the reaction of 4 with nucleophiles to one of the three CO groups. Thus, with the triamide formed from 2-alkyl-4,5-diaryl-oxazoles, CO attack by water or alcohols takes place exclusively at the (less-hindered) CO group derived from the 2-position of the oxazole as shown schematically in 5.

many types of oxidation and reduction, and is capable of yielding the activated carboxyl group under conditions of oxidation which do not affect most functional groups.

There are many situations in organic synthesis where carboxylic acid protecting groups are needed.[5] We have chosen to test the utility of the oxazole-triamide protection method in intramolecular acylation processes leading to lactone formation. In particular, we have shown that this oxidative rearrangement may be utilized in practical, efficient syntheses of macrolides.

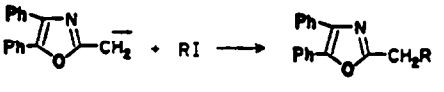
Our procedure for preparing the oxazole substrate is illustrated schematically in Scheme 2 showing the introduction of a side chain containing a nucleophile at the 2-position of 2-methyl-4,5-diphenyloxazole (1). Alternatively, as will be reported later in connection with the synthesis of curvularin, the oxazole utilized as a precursor to the triamide may be constituted directly from benzoin by a standard oxazole synthesis.[6]

2-Methyl-4,5-diphenyloxazole (1) used as a starting material is readily available.[6] Alkylation of the 2-Me group using lithium di-isopropylamide (LDA) at −78° in THF generates the anion (6) which may then be reacted with an alkyl halide (7) as summarized in Table 1. In our general lactone syntheses, the electrophilic species (7) contains an ω-OH group protected as the tetrahydropyranyl ether. After deprotection of the alcohol in acid,



Scheme 2.

Table 1.

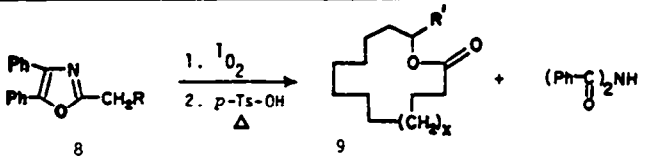


6 7

entry	RI	Yield, %
(a)	CH_3I	73
(b)	$CH_3CH_2CH_2$-I	82
(c)	THPO-$(CH_2)_{11}$-I	57*
(d)	THPO-$(CH_2)_{12}$-I	43*
(e)	THPO-CH(CH_3)-$(CH_2)_{11}$-I	40*
(f)	THPO-CH(CH_3)-CH_2-CH=CH-$(CH_2)_5$-I	43*

Yield of alcohol after hydrolysis of THP ethers

Table 2.



8 9

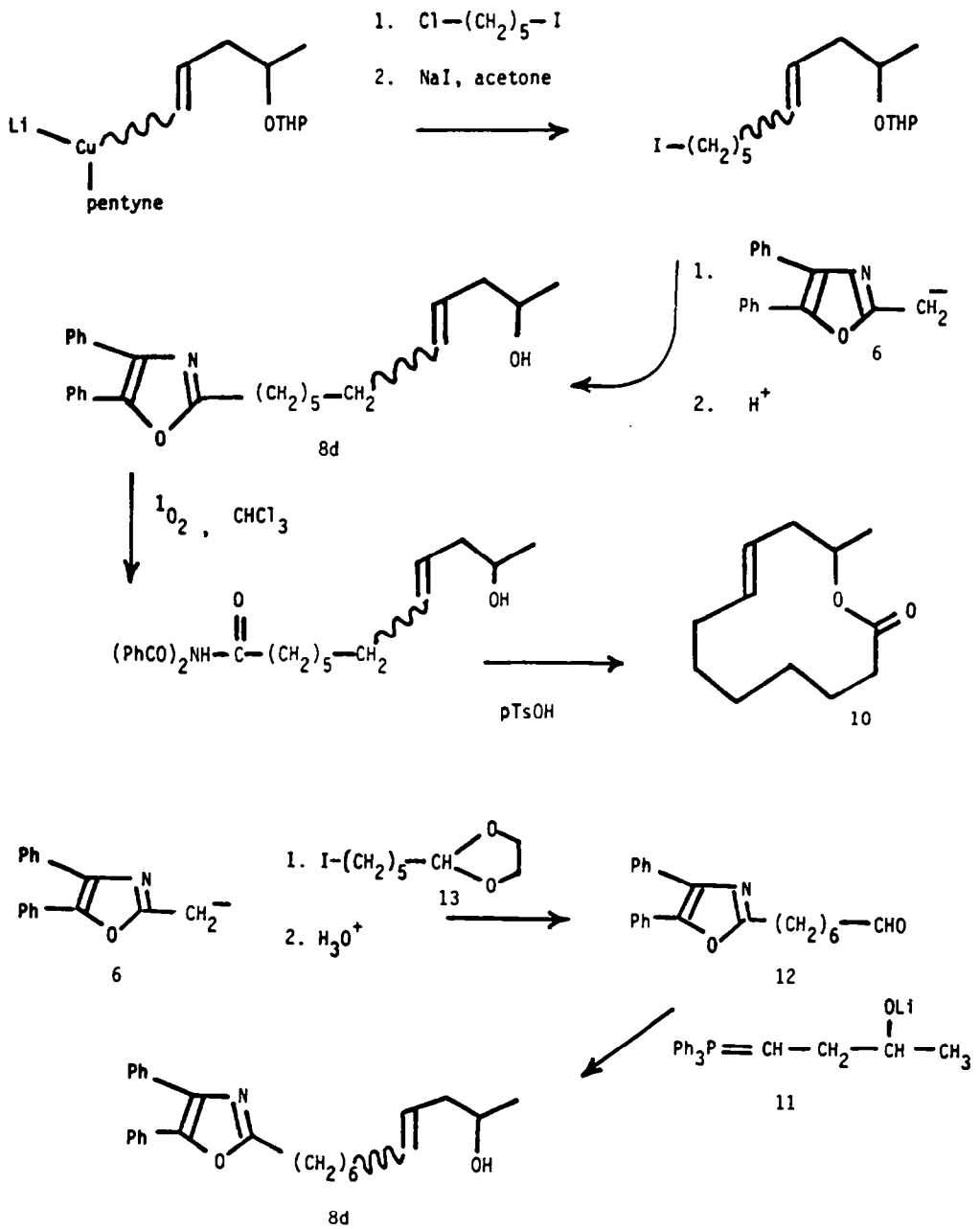
R	Lactone	Yield,%
a;$(CH_2)_{11}$-OH	9a; x=2, R'=H	75
b;$(CH_2)_{12}$-OH	9b; x=3, R'=H	76
c;$(CH_2)_{11}$-CH(CH_3)-OH	9c; x=3, R'=CH_3	64
d;$(CH_2)_5$CH=CHCH$_2$CH(CH_3)-OH	10	55*

mixture of E- and Z-isomers

the resulting hydroxy oxazole (**8**) (Table 2) is allowed to react with singlet oxygen, generated by dye-sensitized photooxygenation (Rose Bengal polymer, 650 w tungsten-halogen light source). Formation of the triamide takes place in high yield, and this intermediate is then allowed to cyclize under conditions of acid catalysis and high dilution.[7] Table 2 summarizes the synthesis of 13-tridecanolide (**9a**),[8] 14-tetradecanolide (**9b**),[9] (±)-14-pentadecanolide (**9c**),[10] and (±)-recifeiolide (**10**).[11,12]

The macrolides prepared as listed in Table 2 were all compared with natural materials. In the case of recifeiolide (**10**), our early synthesis employed the THP ether of 5-tributylstannyl-4-penten-2-ol reported by Corey.[12a] The mixture of *E*- and *Z*-isomers (85:15) obtained in this sequence was converted to the corresponding cuprates by treatment with n-BuLi and 1-pentynylcopper as described. This isomer mixture was then treated with 1-chloro-5-iodopentane and then sodium iodide in acetone to form the iodo-THP ether (entry f, Table 1). Reaction of this product with anion (**6**) followed by acid hydrolysis yielded **8d**. The photooxidation and cyclization of **8d** as shown in Table 2 gave a mixture of *E*- and *Z*-(±)-recifeiolide (**10**) from which the pure *E*-form could be isolated by chromatography on silver nitrate-impregnated silica gel. The synthetic material was identical with natural recifeiolide (NMR, IR, tlc).[13]

In more recent work, we prepared **8d** using the Wittig reaction of the ylide-alkoxide (**11**)[14] with the oxazole-aldehyde (**12**). The latter was obtained by the alkylation of **6** with the acetal of 6-iodohexanal (**13**), followed by hydrolysis in acid. The reaction of **11** with **12** yielded **8d** as a mixture of *E*- and *Z*-isomers (80:20).



Polyether lactones. A second phase of our studies on macrolide synthesis was concerned with the formation of macrocyclic polyether lactones, systems of special current interest because of their unique cation complexing properties. A large variety of macrocyclic polyether-di- or tetra-esters have recently been prepared by Bradshaw[15] and Okahara.[16] Recently, Okahara[16] has developed a method for the formation of 2-oxo-analogues of 18-crown-6 (**14a**) and 15-crown-5 (**14b**). Condensation of the monosodium salt of a polyethylene glycol with sodium bromoacetate at 100°, followed by acidification with HCl and esterification with methanol and sulfuric acid gives the ω-hydroxy ester which is treated with anhydrous sodium carbonate in diglyme at 150° to effect *in situ* macrocyclization in good yields.

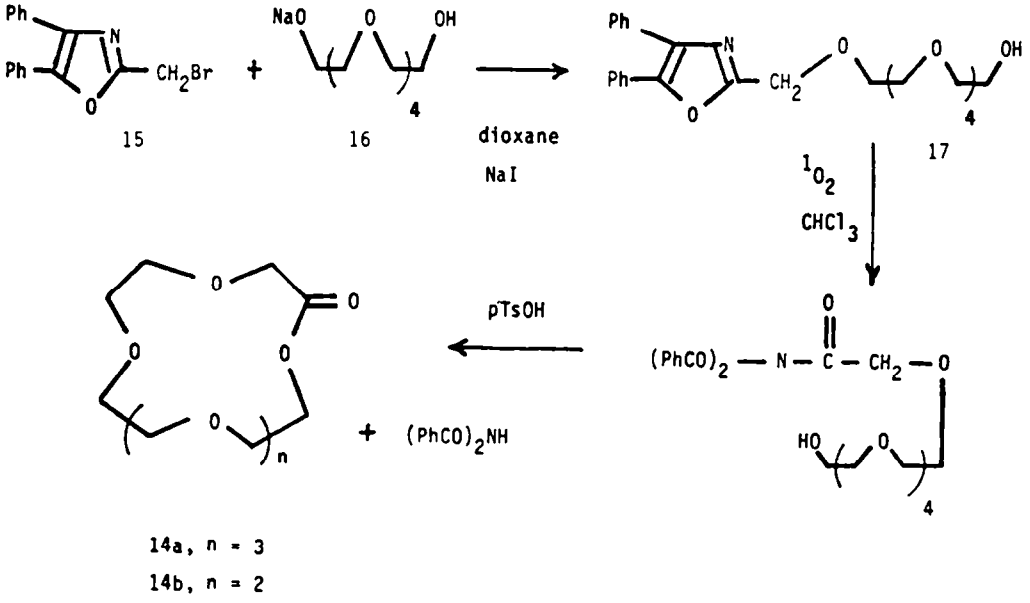
We sought to adapt our method to this synthetic problem as a further example of the utility and efficiency of the oxazole-triamide cyclization procedure. In this instance, the necessary ω-hydroxypolyether-oxazole (**17**) was most readily obtained from the reaction of the monosodium salt of pentaethylene glycol (**16**) and 2-bromomethyl-4,5-diphenyloxazole (**15**)[17] in the presence of sodium iodide. Photooxygenation to the triamide, followed by cyclization as outlined previously gave 2-oxo-18-crown-6 (**14a**) in 46% yield[18] (Scheme 3). Here, again, the oxazole, in the role of a bromoacetate equivalent is transformed to an activated carboxyl group under the mild and selective conditions of photooxygenation. The Okahara synthesis[16] has shown that macrocyclization can be greatly enhanced by constraining the system into a favorable orientation through cationic binding. In continuing work with oxazoles we plan to explore the possibility of improving the yields of lactone formation through a similar mode of cation-assisted cyclization.

Synthesis of (±)-*di*-0-*methylcurvularin.* Extending the use of oxazoles as carboxyl protecting groups and substrates for macrolide synthesis we next turned our attention to the synthesis of derivatives of curvularin (**18**, R = H), a metabolite of the mold species *Curvularia.* The structure and biosynthesis of this 12-membered aromatic lactone was elucidated by Musgrave[19] and Birch,[20] and recent synthetic work on the parent compound and its dimethyl ether has been carried out by Gerlach,[21] Bycroft,[22] and Takahashi.[23] These investigations showed that while this 12-membered keto-lactone system could be formed by an intramolecular acylation reaction, none of the existing procedures for macrocyclic lactone synthesis appeared to be applicable to the cyclization of the dimethyl ether of the hydroxy acid (**19**, R = Me). These methods included use of DCC,[22] trifluoroacetic anhydride,[22] the 2-pyridylthiol ester method with[21] or without silver perchlorate[24] and the t-butylthiol ester procedure.[24]

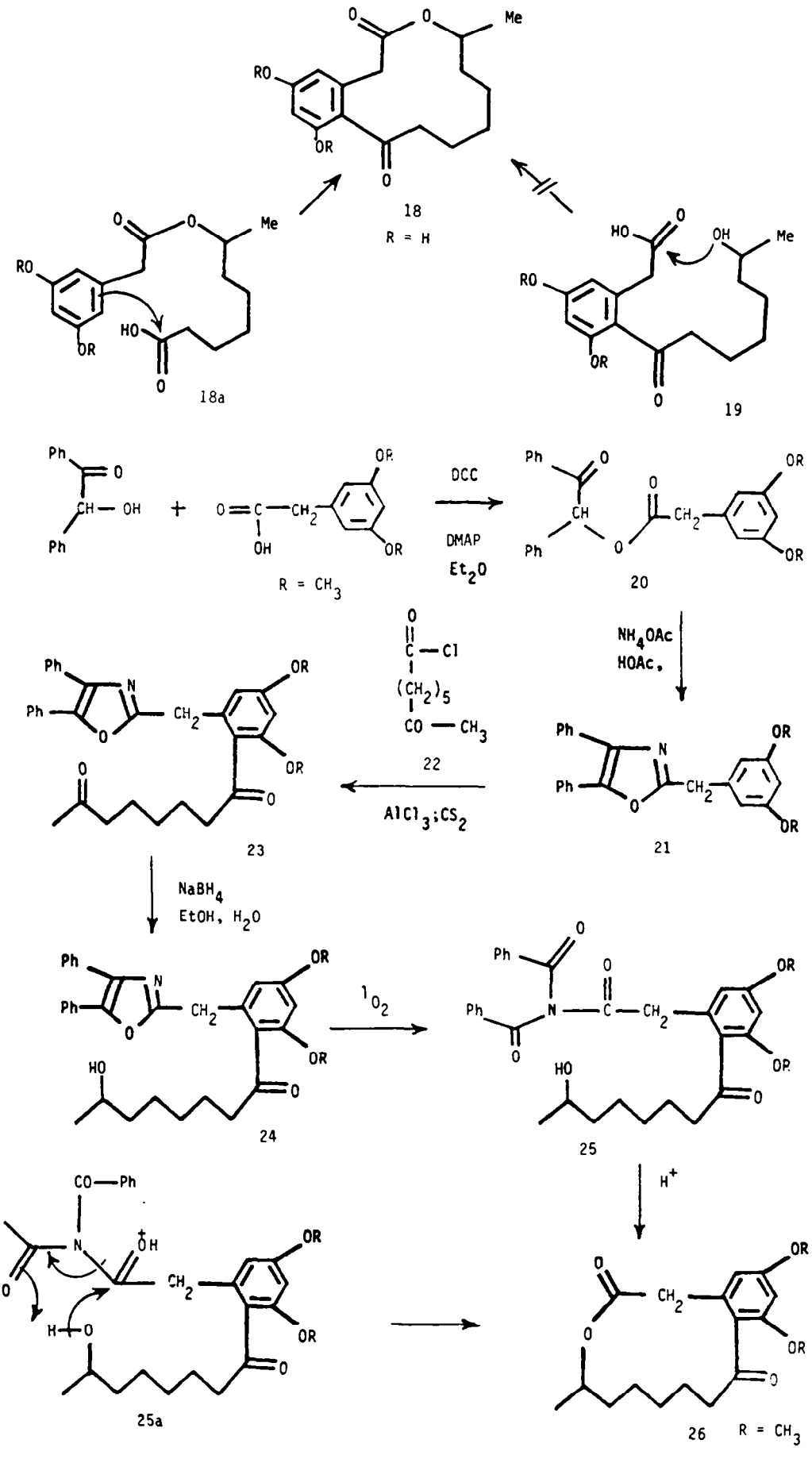
In view of the reported lack of success in achieving intramolecular esterification to curvularin derivatives by the above methods, we decided to test the oxazole-triamide procedure for carboxylate activation as a possible intramolecular esterification route for this case. The successful procedure outlined below represents the first instance of internal esterification in the preparation of the curvularin system.

The aromatic portion of the molecule was derived from the readily available methyl 3,5-dimethoxyphenylacetate.[25] This acetate was converted to the required oxazole (**21**) (68% yield) in standard fashion by (a) hydrolysis in ethanolic KOH, (b) esterification with benzoin to form **20** using DCC in the presence of 4-dimethylaminopyridine (DMAP)[26] and (c) treatment with excess ammonium acetate in refluxing glacial acetic acid. Friedel–Crafts acylation[27] of **21** with 7-oxo-octanoyl chloride (**22**)[21] provided the diketo-oxazole (**23**) (50%), which underwent selective reduction of the aliphatic carbonyl with $NaBH_4$[28] in nearly quantitative yield forming the hydroxyoxazole (**24**).

When the hydroxyoxazole (**24**) was subjected to dye-sensitized photooxygenation (Sensitox), it was readily converted to the corresponding triamide (**25**) which underwent acid-catalyzed cyclization (30%) in refluxing benzene to yield (±)-di-0-methylcurvularin (**26**). The



Scheme 3.


18
R = H
18a
19
R = CH3
DCC
DMAP
Et2O
20
NH4OAc
HOAc,
22
AlCl3;CS2
21
23
NaBH4
EtOH, H2O
1O2
24
25
H+
25a
26
R = CH3

product (**26**) was shown to be completely identical (NMR, IR, tlc) with an authentic sample.[24]

We suggest that the triamide activation route for macrolide formation provides an interesting example of a "double activation"[29] process as portrayed in structure **25a**, where the benzoyl groups may participate in proton removal through a 6-membered transition state. We are currently investigating the application of this type of reaction sequence for the synthesis of other macrolides of biological interest.

EXPERIMENTAL

Tetrahydropyranyl ether of 11-*iodo*-1-*hydroxyundecane* (**7c**). To a soln of 11-bromo-1-hydroxyundecane (5.02 g; 0.020 mole) in THF (75 mL) was added dihydropyran (1.68 g; 0.020 mole) and *p*-toluene-sulfonic acid (50 mg). The mixture was stirred for 1 hr at room temp and the solvent was removed *in vacuo* until about 15 mL remained, whereupon the mixture was poured into water and extracted twice with ether. The organic layers were combined, washed with a sat $NaHCO_3$ aq, a sat NaCl aq, and dried over $MgSO_4$. The solvent was removed *in vacuo* leaving an oil which was immediately dissolved in acetone (100 mL). To this soln was added NaI (12 g; 0.080 mole) and the mixture was stirred at room temp for 24 hr. The ppt was then filtered, the solvent was removed *in vacuo* and the residue was taken up in ether, washed with water, once with 5% $Na_2S_2O_3$ aq, a sat NaCl aq and dried over $MgSO_4$. The solvent was removed *in vacuo* leaving **7c** (6.28 g; 82%) as a light yellow oil.

IR (neat) 2940, 2860, 1460, 1440, 1355, 1215, 1140, 1130, 1090, 1040, 975 cm^{-1}; NMR ($CDCl_3$) δ 4.5–4.6 (*m*, 1H), 3.3–4.0 (*m*, 6H), 3.17 (*t*, J = 7.0 Hz, 2H), 1.2–1.9 (*m*, 24H).

2-(12-*Hydroxydodecanyl*)-4,5-*diphenyloxazole* (**8a**). To a soln of diisopropylamine (0.44 g; 4.31 mmole) in THF (10 mL) at 0° was added n-BuLi in hexane (1.87 mL; 4.31 mmole of a 2.3 M soln). The soln was stirred an additional 20 min at 0°, cooled to −78° and treated with a soln of 2-methyl-4,5-diphenyloxazole (1.013 g; 4.31 mmole) in THF (10 mL) over 30 min. The carmine red mixture was stirred for an additional 30 min at −78°, and then a soln of **7c** (1.647 g; 4.31 mmole) in THF (5 mL) was added all at once. The mixture was allowed to warm to room temp over 4 hr and then quenched with water. The solvent was removed *in vacuo* and the residue was taken up in ether, washed three times with water, once with a sat NaCl aq and dried over $MgSO_4$. The solvent was removed *in vacuo* leaving an oil which was dissolved in a 1:1 MeOH–AcOH mixture (100 mL). The mixture was stirred at 60° for 12 hr and the solvent was then removed *in vacuo* leaving a yellow oil. Flash chromatography using a 1:1 ether–hexane mixture (R_f = 0.2) gave **8a** (0.838 g; 48%) as an oil which solidified (m.p. 66–67°, ether–hexane) on standing.

IR (KBr) 3350, 3070, 2960, 2880, 1565, 1450, 1085 cm^{-1}; NMR ($CDCl_3$) δ 7.5–7.7 (*m*, 4H), 7.2–7.4 (*m*, 6H), 3.55 (*t*, J = 6.5 Hz, 2H), 2.83 (*t*, J = 7.5 Hz, 2H), 1.2–1.6 (*m*, 20H). MS (70 eV) *m/e*: 406, 405 (M^+), 290, 249, 248, 236, 235 (base). (Found: C, 79.90; H, 8.68; N, 3.41. Calc. for $C_{27}H_{35}NO_2$: C, 79.96; H, 8.70; N, 3.45%).

13-*Hydroxytridecanoic acid lactone* (**9a**). A soln of **8a** (405 mg; 1.00 mmole) in CH_2Cl_2 (100 mL) was oxygenated in the presence of Sensitox (Rose Bengal polymer) (40 mg) during irradiation with a tungsten–halogen light source (650 w) for 30 min. After filtration of the Sensitox and removal of the solvent *in vacuo*, the triamide was obtained as an oil. The oil was dissolved in benzene (35 mL) and added dropwise to a refluxing mixture of *p*-toluenesulfonic acid (25 mg) in benzene (100 mL) over 24 hr. The mixture was then cooled and the solvent was removed *in vacuo* leaving a yellow residue. Flash chromatography using a 1:9 ether–hexane mixture gave **9a** (160 mg; 75%) as a clear oil which was identified by comparison with an authentic sample (IR, NMR, tlc).

12-*Bromo*-1-*hydroxydodecane*. To a soln of 12-bromododecanoic acid (2.8 g; 0.010 mole) in THF (20 mL) at 0° was added dropwise borane in THF (15 mL; 0.015 mole of a 0.98 M soln). The mixture was warmed to room temp and stirred for 2 hr. The mixture was quenched by slowly adding a solution of conc HCl in MeOH. The solvent was removed *in vacuo* and the residue was taken up in ether, washed once with water, once with a sat $NaHCO_3$ aq, once with a sat NaCl aq and dried over $MgSO_4$. The solvent was removed *in vacuo* leaving 12-bromo-1-hydroxydodecane (2.5 g; 96%) as a clear oil.

IR (neat) 3350, 2940, 1480, 1075, 800 cm^{-1}; NMR ($CDCl_3$) δ 3.61 (*t*, J = 6.0 Hz, 2H), 3.38 (*t*, J = 6.5 Hz, 2H), 1.2–2.0 (*m*, 21H).

Tetrahydropyranyl ether of 12-*iodo*-1-*hydroxydodecane* (**7d**). This compound was prepared by the same procedure as that employed in the preparation of **7c**. The reagents used in the preparation were: 12-bromo-1-hydroxydodecane (2.50 g; 0.0094 mole), dihydropyran (0.81 g; 0.010 mole), *p*-toluenesulfonic acid (25 mg), THF (40 mL), NaI (5.8 g; 0.38 mole) and acetone (50 mL). The product **7d** (3.0 g; 78%) was obtained as a light yellow oil.

IR (neat) 2940, 2870, 1460 cm^{-1}; NMR ($CDCl_3$)δ 4.5–4.6 (*m*, 1H), 3.3–4.0 (*m*, 6H), 3.18 (*t*, J = 7.0 Hz, 2H), 1.2–1.9 (*m*, 26H).

2-(13-*Hydroxytridecanyl*)-4,5-*diphenyloxazole* (**8b**). This compound was prepared by the same procedure as that employed in the preparation of **8a**. The reagents used in the preparation were: diisopropylamine (0.76 g; 7.53 mmole), THF (10 mL), n-BuLi in hexane (3.27 mL, 7.53 mmole of a 2.30 M soln), 2-methyl-4,5-diphenyloxazole (1.77 g; 7.53 mmole), THF (30 mL), compound **7d** (2.98 g; 7.53 mmol), THF (10 mL), and a 1:1 MeOH–AcOH mixture (100 mL). Flash chromatography using a 1:1 ether–hexane mixture (R_f = 0.2) gave **8b** (1.39 g; 44%) as an oil which solidified (m.p. 71–72.5°, ether–hexane) on standing. IR (KBr) 3350, 3075, 2970, 2880, 1565, 1450, 1080 cm^{-1}; NMR ($CDCl_3$) δ 7.5–7.7 (*m*, 4H), 7.2–7.4 (*m*, 6H), 3.58 (*t*, J = 6.5 Hz, 2H), 2.84 (t, J = 7.5 Hz, 2H), 1.2–1.6 (*m*, 22H). MS (70 eV) *m/e* 420, 419 (M^+) 290, 249, 248, 235 (base). (Found: C, 79.98; H, 8.79; N, 3.24. Calc. for $C_{28}H_{37}NO_2$: C, 80.15; H, 8.89; N, 3.34%).

14-*Hydroxytetradecanoic acid lactone* (**9b**). This compound was prepared by the same procedure as that employed in the preparation of **9a**. The reagents used in the preparation were: **8b** (419 mg; 1.00 mmole), CH_2Cl_2 (100 mL), Sensitox (40 mg), benzene (35 mL), *p*-toluenesulfonic acid (25 mg), and benzene (100 mL). Flash chromatography using a 1:9 ether–hexane mixture gave **9b** (172 mg; 76%) as a clear oil which was identified by comparison with an authentic sample (IR, NMR, tlc).

12-*Bromododecanal*. To a vigorously stirred suspension of pyridinium chlorochromate (3.24 g; 0.015 mole) and Celite (3 g) in CH_2Cl_2 (50 mL) was added 12-bromo-1-hydroxydodecane (2.65 g; 0.010 mole). The mixture was stirred for 1.5 hr and then diluted with anhyd ether (100 mL). The ppt was filtered off and washed three times with ether. The combined filtrate was removed *in vacuo* leaving a brown residue. Silica gel chromatography using ether gave 12-bromododecanal (2.16 g; 82%) as a clear oil.

IR (neat) 2940, 1730, 1470 cm^{-1}; NMR ($CDCl_3$) δ 9.77 (*t*, J = 2.0 Hz, 1H), 3.40 (*t*, J = 6.5 Hz, 2H), 2.43 (*dt*, J = 2.0 Hz and 6.5 Hz, 2H), 1.2–2.0 (*m*, 18H).

13-*Bromo*-2-*hydroxytridecane*. To a soln of 12-bromododecanal (2.10 g; 8.0 mmole) in ether (50 mL) at 0° was added MeMgBr in ether (2.9 mL; 9.0 mmole of a 3.1 M soln). The soln was allowed to warm to room temp and stirred for 16 hr. The mixture was then quenched with a sat NH_4Cl aq and the organic layer was separated, washed four times with water, once with a sat NaCl aq and dried over $MgSO_4$. The solvent was removed *in vacuo* leaving 13-bromo-2-hydroxytridecane (1.95 g; 87%) as a clear oil.

IR (neat) 3350, 2960, 2880 cm^{-1}. NMR ($CDCl_3$) δ 3.6–3.9 (*m*, 1H), 3.41 (*t*, J = 6.5 Hz, 2H), 1.2–1.9 (*m*, 21H), 1.20 (*d*, J = 6.0 Hz, 3H).

Tetrahydropyranyl ether of 13-*iodo*-2-*hydroxytridecane* (**7e**). This compound was prepared by the same procedure as that employed in the preparation of **7c**. The reagents used in the preparation were: 13-bromo-2-hydroxytridecane (1.85 g; 6.63 mmole), dihydropyran (0.60 g; 7.. mmole), *p*-toluene sulfonic acid (10 mg), THF (50 mL), NaI (9.0 g; 60 mmole) and acetone (50 mL). The product **7e** (1.84 g; 64%) was obtained as a clear oil.

IR (neat) 2950, 2870, 1475, 1135, 1090, 1040 cm^{-1}; NMR ($CDCl_3$) δ 4.6–4.8 (*m*, 1H), 3.3–4.1 (*m*, 3H), 3.18 (*t*, J = 7.0 Hz, 2H), 1.1–1.9 (*m*, 29H).

2-(13-*Hydroxytetradecanyl*)-4,5-*diphenyloxazole* (**8c**). This

compound was prepared by the same procedure as that employed in the preparation of **8a**. The reagents used in the preparation were: diisopropylamine (122 mg; 1.21 mmole), THF (10 mL), n-BuLi in hexane (0.58 mL; 1.21 mmol of a 2.1 M soln), 2-methyl-4,5-diphenyloxazole (284 mg; 1.21 mmole), THF (15 mL), compound **7e** (498 mg; 1.21 mmol), THF (5 mL), and a 1:1 MeOH–AcOH mixture (50 mL). Flash chromatography using a 1:1 ether–hexane mixture (R_f = 0.25) gave **8c** (204 mg; 39%) as an oil which solidified (m.p. 57–58°, ether–hexane) on standing.

IR (KBr) 3350, 3075, 2960, 2885, 1570, 1445, 1080 cm^{-1}; NMR ($CDCl_3$) δ 7.5–7.7 (*m*, 4H), 7.2–7.4 (*m*, 6H), 3.6–3.9 (*m*, 1H), 3.81 (*t*, J = 7.5 Hz, 2H), 1.2–1.5 (*m*, 22H), 1.15 (*d*, J = 6.5 Hz, 3H). MS (70 eV) *m/e* 433 (M^+), 248 236, 235 (base). (Found: C, 80.17; H, 8.99; N, 3.33. Calc. for $C_{29}H_{39}NO_2$: C, 80.33; H, 9.07; N, 3.23%).

(±)-14-*Hydroxypentadecanoic acid lactone* (**9c**). This compound was prepared by the same procedure as that employed in the preparation of **9a**. The reagents used in the preparation were: **8c** (184 mg; 0.425 mmol), CH_2Cl_2 (100 mL), Sensitox (40 mg), benzene (35 mL), *p*-toluenesulfonic acid (10 mg), and benzene (100 mL). Flash chromatography using a 1:19 ether–hexane mixture gave **9c** (65 mg; 64%) as a clear oil which was identified by comparison with an authentic sample (IR, NMR, tlc).

6-*Chlorohexanal*. To a mixture of pyridinium chlorochromate (16.2 g; 0.075 mol) and Celite (16 g) in CH_2Cl_2 (100 mL) was added 6-chloro-1-hydroxyhexane (6.85 g, 0.050 mole) with vigorous stirring. The mixture was stirred for 1.5 hr then diluted with anhyd ether (200 mL). The mixture was filtered and the filtrate was removed *in vacuo*. Silica gel chromatography of the residue, followed by distillation (38–40°, 0.4 mm Hg) gave 6-chlorohexanal as a clear oil (4.32 g; 64%).

IR (neat) 2960, 2890, 2750, 1730, 1470, 1455 cm^{-1}; NMR ($CDCl_3$) δ 9.77 (*t*, J = 1.5 Hz, 1H), 3.52 (*t*, J = 6.5 Hz, 2H), 2.45 (*dt*, J = 1.5 Hz and 6.0 Hz, 2H), 1.3–2.0 (*m*, 6H).

2-(5-*Iodopentyl*)-1,3-*dioxolane* (**13**). To a soln of 6-chlorohexanal (4.05 g; 0.030 mol) in acetone (50 mL) was added a soln of NaI (22.5 g; 0.15 mol) in acetone (50 mL). The mixture was stirred at reflux for 36 hr, then cooled and the ppt was filtered. The filtrate was removed *in vacuo* and the residue was taken up in ether, washed twice with water, once with a 5% $Na_2S_2O_3$ aq, a sat NaCl aq and dried over $MgSO_4$. The solvent was removed *in vacuo* leaving a clear oil which was dissolved in benzene (20 mL) and added to a mixture of ethylene glycol (9.3 g; 0.15 mol) and *p*-toluenesulfonic acid (50 mg) in benzene (200 mL). The mixture was refluxed using a Dean–Stark trap for 24 hr, then cooled. The organic layer was washed once with a sat $NaHCO_3$ aq, four times with water, once with a sat NaCl aq and dried over $NaSO_4$. The solvent was removed *in vacuo* leaving a clear oil which was identified as **13** (7.51 g; 93%).

NMR ($CDCl_3$) δ 4.84 (*t*, J = 4.0 Hz, 1H), 3.7–4.0 (*m*, 4H), 3.16 (*t*, J = 7.0 Hz, 2H), 1.3–2.0 (*m*, 8H).

2-(7-*Oxoheptyl*)-4,5-*diphenyloxazole* (**12**). To a soln of diisopropylamine (0.56 g; 5.50 mmol) in THF (10 mL) at 0° was added n-BuLi in hexane (2.4 mL; 5.50 mmol of 2.3 M soln). The soln was stirred 20 min at 0°, cooled to −78° and treated with a soln of 2-methyl-4,5-diphenyloxazole (1.18 g; 5.00 mmol) in THF (30 mL) over 1 hr. To the carmine red soln was added hexamethylphosphoric triamide (1 mL; 5.5 mmol) and then a soln of **13** (1.49 g; 5.50 mmol) in THF (5 mL). The soln was allowed to warm to room temp over 4 hr and quenched with water. The solvent was removed *in vacuo* and the residue was taken up in ether, washed four times with water, once with a sat NaCl aq and dried over $MgSO_4$. The solvent was removed *in vacuo* leaving an oil which was dissolved in a mixture of THF (50 mL), water (50 mL) and conc HCl (5 ml). The mixture was stirred at 60–70° for 1 hr and the THF was removed *in vacuo*. The aqueous layer was extracted three times with ether, the organic layers were combined, washed three times with water, once with a sat NaCl aq, dried over $MgSO_4$ and the solvent removed *in vacuo* leaving an oil. Flash chromatography using a 3:7 ether–hexane mixture (R_f = 0.1) gave **12** (1.03 g; 62%) as a yellow oil.

IR (neat) 3055, 2935, 2855, 1725, 1575, 1450, 1045 cm^{-1}. NMR ($CDCl_3$) δ 9.80 (*t*, J = 1.5 Hz, 1H), 7.5–7.7 (*m*, 4H), 7.2–7.4 (*m*, 6H), 2.84 (*t*, J = 7.5 Hz), 2.43 (*dt*, J = 1.5 Hz and 6.0 Hz, 2H), 1.3–2.0 (*m*, 8H).

2-(10-*Hydroxy*-7-*undecenyl*)-4,5-*diphenyloxazole* (**8d**). To a suspension of triphenylphosphonium bromide (357 mg; 1.00 mmol) in THF (10 mL) was added n-BuLi in hexane (0.48 mL; 1.10 mmol of a 2.3 M soln) at 0°. The mixture was warmed to room temp and stirred for 1 hr. To the yellow soln at 0° was added propylene oxide (64 mg; 1.10 mmol) and the mixture was stirred for 2 hr, then treated with n-BuLi in hexane (0.43 ml; 1.00 mmol of a 2.3 M soln). The mixture was stirred for 1 hr at 0°, cooled to −45° and treated with **12** (333 mg; 1.00 mmol) in THF (5 mL). The yellow mixture was stirred 1 hr at −45°, warmed to room temp and stirred for 4 hr, then quenched with water. The solvent was removed *in vacuo* leaving a residue which was taken up in ether, washed twice with a 1 N HCl, twice with water, once with a sat NaClaq, dried over $MgSO_4$ and the solvent removed *in vacuo* leaving an oil. Flash chromatography using a 1:1 ether–hexane mixture gave an 80:20 mixture of the *E*- and *Z*-isomers of **8d** (201 mg; 52%) as a yellow oil (R_f = 0.2).

IR (neat) 3350, 3060, 3030, 2940, 2870, 1575, 1460, 1075, 980 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 7.56–7.67 (*m*, 4H), 7.30–7.41 (*m*, 6H), 5.34–5.59 (*m*, 2H), 3.72–3.85 (*m*, 1H), 2.85 (*t*, J = 7.7 Hz, 2H), 1.80–2.22 (*m*, 4H), 1.34–1.53 (*m*, 8H), 1.20 (*d*, J = 6 Hz (*Z*-isomer)) and 1.18 (*d*, J = 5.9 Hz (*E*-isomer), 3H). MS (70 eV) *m/e* 389 (M^+), 345, 344, 249, 248 (base), 235.

Tetrahydropyranyl ether of 10-*iodo*-4-*decene*-2-*ol* (**7f**). To a soln of the tetrahydropyranyl ether of 5-tributylstannyl-4-penten-2-ol (3.433 g; 7.48 mmol) in THF (100 mL) at −78° was added *n*-BuLi in hexane (3.48 mL; 7.48 mmol of a 2.15 M soln). The soln was stirred for 2 hr at −78° and then for 1 hr at −10°. A second soln was prepared under N_2 at room temp containing 1-pentynyl copper (1.02 g; 7.75 mmol) and hexamethylphosphorous triamide (2.53 g; 15.5 mmol) in THF (10 mL). After 5 min stirring, the latter soln was added to the first soln of alkenyllithium which had been cooled to −78°. The light green soln which resulted was stirred for 2 hr at −78°, 1 hr at −45° and was then treated at −78° with 1-chloro-5-iodopentane (3.61 g; 15.5 mmol). The mixture was stirred for 3 hr at −78° and then allowed to warm to room temp over 12 hr. The mixture was then quenched with water and the THF was evaporated *in vacuo*. The residue was taken up in ether, washed with a sat NH_4Cl aq in NH_4OH aq, then with a sat NaOAc in aqueous AcOH soln. These washings were repeated carefully and then the organic layer was washed twice with water, once with a sat NaCl aq and dried over $MgSO_4$. The solvent was removed *in vacuo*, leaving an oil which was dissolved in acetone (25 mL) and then treated with a soln of NaI (6.0 g; 40 mmol) in acetone (150 mL). The mixture was then refluxed for 30 hr, cooled and the ppt filtered off. The solvent was removed *in vacuo* and the residue was taken up in ether, washed twice with water, once with a 5% NaS_2O_3 aq, once with a sat NaCl aq, dried over $MgSO_4$ and the solvent removed *in vacuo* leaving a yellow oil. Flash chromatography using a 1:9 ether–hexane mixture gave an 85:15 mixture of the *E*- and *Z*-isomers of **7f** (1.517 g; 55%) as an oil (R_f = 0.3).

IR (neat) 2940, 2860, 1140, 1090, 1030, 1010 cm^{-1}; NMR ($CDCl_3$) δ 5.3–5.5 (*m*, 2H), 4.6–4.7 (*m*, 1H), 3.3–4.0 (*m*, 3H), 3.15 (*t*, J = 7.0 Hz, 2H), 1.0–2.3 (*m*, 19H).

2-(10-*Hydroxy*-7-*undecenyl*)-4,5-*diphenyloxazoie* (**8d**). This compound was prepared by the same procedure as that employed in the preparation of **8a**. The reagents used in the preparation were: diisopropylamine (185 mg; 1.83 mmol), THF (5 mL), n-BuLi in hexane (0.85 mL; 1.83 mmol of a 2.15 M soln), 2-methyl-4,5-diphenyloxazole (430 mg; 1.83 mmol), THF (10 mL), compound **7f** (668 mg; 1.83 mmol), THF (5 mL) and a 1:1 MeOH–AcOH mixture (80 mL). Flash chromatography using a 1:1 ether–hexane mixture (R_f = 0.2 gave an 85:15 mixture of the *E*- and *Z*-isomers of **8d** (305 mg; 43%) as a yellow oil.

Recifeiolide (**10**). This compound was prepared by the same procedure as that employed in the preparation of **9a**. The reagents used in the preparation were: **8d** (458 mg; 1.18 mmol), CH_2Cl_2 (100 mL), Sensitox (40 mg), benzene (35 mL), *p*-toluenesulfonic acid (20 mg), and benzene (100 mL). Flash chromatography using a 1:24 ether–hexane mixture gave **10** (127 mg; 55%) as an 85:15 mixture of the *E*- and *Z*-isomers. A sample of the pure *E*-isomer could be obtained by chromatography of the mixture on $AgNO_3$-impregnated silica gel using a

1:3 ether–hexane mixture. This isomer was identical in all respects with an authentic sample of the material (IR, NMR, tlc).

Pentaethylene glycol mono-2-methyl-4,5-diphenyloxazole ether (**17**). To a MeOH soln (50 mL) containing NaOMe (216 mg; 4.00 mmol), pentaethylene glycol (3.178 g; 13.33 mmol) was added. The soln was stirred for 20 min at 40°, and then the MeOH was evaporated *in vacuo*. The residue was dissolved in *p*-dioxane (100 mL), then **15** (1.256 g; 4.00 mmol) and NaI (50 mg) were added, and the mixture was refluxed for one day. *p*-Dioxane was evaporated *in vacuo*, then the residue was taken up in CH_2Cl_2, washed four times with water, and the organic layer was evaporated *in vacuo* without the use of a pre-drying agent, to a yellow oil. Flash chromatography using a 5:95 MeOH–ether mixture gave **17** (1.145 g; 61%) as a light yellow oil.

IR ($CHCl_3$) 3475 cm^{-1}; NMR ($CDCl_3$) δ 7.5–7.7 (*m*, 4H), 7.2–7.4 (*m*, 6H), 4.68 (s, 2H), 3.50–3.78 (br *m*, 20H). (Found: p^+, 471.226. Calc. for $C_{26}H_{33}NO_7$: p^+, 471.226).

2-Oxo-18-crown-6 (**14a**). This compound was prepared by the same procedure as that employed in the preparation of **9a**. The reagents used in the preparation were: **17** (626 mg; 1.31 mmol), CH_2Cl_2 (10 mL), Sensitox (40 mg), benzene (35 mL), *p*-toluenesulfonic acid (50 mg), and benzene (100 mL). Flash chromatography using a 1:9 MeOH–CH_2Cl_2 mixture followed by Kugelrohr distillation gave **14a** (168 mg; 46%) as a light yellow oil which was identified by comparison with an authentic sample (IR, NMR, *m/e*, TLC, GPC).

Benzoin 3,5-dimethoxyphenyl acetate (**20**). To a soln of methyl 3,5-dimethoxyphenylacetate (2.10 g; 10 mmol) in 95% EtOH (25 mL) was added a soln of KOH (1.00 g; 15 mmol) in 95% EtOH (50 mL) over 30 min. The mixture was stirred an additional hr and the EtOH was removed *in vacuo*. The residue was dissolved in water and acidified to pH 3 with 2 N H_2SO_4 to precipitate 3,5-dimethoxyphenyl acetic acid. The mixture was filtered, and the crude yellow solid was air-dried overnight. A mixture of the crude solid, benzoin (1.93 g; 9.09 mmol), N,N'-dicyclohexylcarbodiimide (1.88 g; 9.09 mmol), and 4-dimethylaminopyridine (10 mg; 0.83 mmol) was stirred in anhyd ether (45 mL) for 5.5 hr at room temp. The mixture was diluted with ether and filtered. The filtrate was washed twice with a 5% HCl, a sat $NaHCO_3$ aq and a sat NaCl aq. The ether layer was dried over $MgSO_4$ and evaporated *in vacuo* to give an oil. Gradient elution chromatography in an ether:petroleum ether mixture (1:4 to 1:1) gave **20** as a light yellow oil (3.21 g; 82%) which solidified on standing.

IR ($CHCl_3$) 1738, 1695 cm^{-1}; NMR ($CDCl_3$) δ 7.86 (*m*, 2H), 7.10–7.45 (*m*, 8H), 6.87 (*s*, 1H), 6.47 (*d*, J = 2 Hz, 2H), 6.34 (*d*, J = 2 Hz, 1H), 3.66 (*s*, 2H), 3.58 (*s*, 6H). (Found: p^+, 390.148. Calc. for $C_{24}H_{22}O_5$: p^+, 390.147).

2-(3,5-Dimethoxyphenylmethyl)-4,5-diphenyloxazole (**21**). A mixture of **20** (3.21 g; 8.22 mmol) and NH_4OAc (3.17 g; 41.10 mmol) in glacial AcOH (12 mL) was refluxed for 1.5 hr. The addition of water (100 mL) produced an oil which was extracted with three portions of benzene. The benzene extracts were combined and filtered through a $MgSO_4$ pad, and the benzene was removed *in vacuo* to give a yellow oil. Flash chromatography using a 15:85 ether–petroleum ether mixture gave **21** (2.53 g; 83%) as a yellow oil which crystallized from MeOH (m.p. 78°).

IR ($CHCl_3$) 1605 cm^{-1}; NMR ($CDCl_3$) δ 7.5–7.7 (*m*, 4H), 7.2–7.4 (*m*, 6H), 6.59 (*d*, J = 2 Hz, 2H), 6.42 (*d*, J = 2 Hz, 1H), 4.12 (*s*, 2H), 3.78 (*s*, 6H). MS (70 eV) *m/e* 372, 371 (m^+, base), 370, 165. (Found: C, 77.50; H, 5.64; N, 3.75. Calc. for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77%).

2 - (3,5 - Dimethoxy - 2 - (1',7' - dioxooctyl) - phenylmethyl) - 4,5 - diphenyloxazole **23**). To a mixture of anhyd $AlCl_3$ (317 mg; 2.21 mmol) in CS_2 (1.0 mL) was added **22** (265 mg; 1.50 mmol) in CS_2 (1.0 mL) at 0° with vigorous mechanical stirring. A soln of **21** (349 mg; 0.94 mmol) in CS_2 (2.0 mL) was added over 5 min dropwise, and the mixture was stirred vigorously for 2 days at 0–20°. The mixture was poured onto a mixture of ice and 1 N HCl and extracted with CH_2Cl_2. The aqueous layer was further acidified with conc HCl acid and extracted three times with CH_2Cl_2. The combined organic layers were washed twice with a sat $NaHCO_3$ aq, once with water, dried over Na_2SO_4 and evaporated *in vacuo* to give an oil. Flash chromatography using a 2:3 ether–petroleum ether mixture gave **23** (229 mg; 50%) as a yellow oil.

IR ($CHCl_3$) 1715, 1690, 1610 cm^{-1}; NMR ($CDCl_3$) δ 7.5–7.7 (*m*, 4H), 7.2–7.4 (*m*, 6H), 6.53 (*d*, J = 2 Hz, 1H), 6.39 (*d*, J = 2 Hz, 1H), 4.18 (s, 2H), 3.79 (*s*, 6H), 2.85 (*t*, J = 7 Hz, 2H), 2.33 (*t*, J = 7 Hz, 2H), 2.06 (*s*, 3H), 1.26–1.73 (*m*, 6H). (Found: p^+, 511.237. Calc. for $C_{32}H_{33}NO_5$: p^+, 511.236).

2 - (3,5 - Dimethoxy - 2 - (7' - hydroxy - 1' - oxooctyl) - phenylmethyl) - 4,5 - diphenyloxazole (**24**). To a soln of **23** (272 mg; 0.53 mmol) in EtOH (2.0 mL) was added a soln of $NaBH_4$ (35 mg; 0.93 mmol) in water (3.0 mL). Additional EtOH (1.5 mL) was added, and the mixture was kept at room temp for 30 min with occasional vigorous shaking. The mixture was acidified to pH 3 with 2 N H_2SO_4, diluted with water and extracted four times with ether. The combined ether layers were dried over $MgSO_4$, and solvent was removed *in vacuo* to give a yellow oil. Flash chromatography using a 2:3 ether–hexane mixture gave **24** (265 mg; 94%) as a light yellow oil.

IR ($CHCl_3$) 3600, 1685, 1610 cm^{-1}; NMR ($CDCl_3$) δ 7.5–7.7 (*m*, 4H), 7.2–7.4 (*m*, 6H), 6.52 (*d*, J = 2 Hz, 1H), 6.39 (*d*, J = 2 Hz, 1H), 4.18 (*s*, 2H), 3.78 (*s*, 6H), 2.84 (*t*, J = 8 Hz, 2H), 1.19–1.65 (*m*, 8H), 1.11 (*d*, J = 6 Hz, 3H). (Found: p^+, 513.253. Calc. for $C_{32}H_{35}NO_5$: p^+, 513.252).

(±)-Di-O-methyl-curvularin (**25**). This compound was prepared by the same procedure as that employed in the preparation of **9a**. The reagents used in the penetration were: **24** (265 mg; 0.52 mmol), $CHCl_3$ (100 mL), Sensitox (40 mg), benzene (35 mL), *p*-toluene sulfonic acid (25 mg), and benzene (100 mL). Flash chromatography using a 1:4 ether–hexane mixture followed by Kugelrohr distillation gave **25** (52 mg, 31%) as a light yellow oil which was shown to be completely identical with an authentic sample (IR, NMR, *m/e*, TLC, GPC).

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