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A Simple, Short, and Flexible Synthesis of Viridiofungin Derivatives

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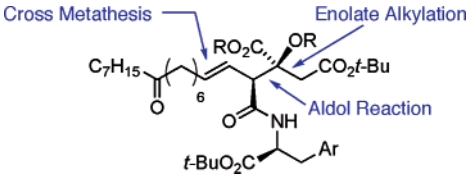

Described herein is a simple, flexible, and efficient synthesis of the skeleton of the viridiofungins, a family of microbial secondary metabolites. The synthesis utilizes an asymmetric aldol reaction of a chiral oxazolidinone, a diastereoselective alkylation of a chiral 1,3-dioxolan-2-one, and a geometrically selective alkene cross-metathesis reaction as the key C−C bond-forming steps.

Introduction

The viridiofungins, a family of aminoacyl vinyl citrate antibiotics, which are exemplified by viridiofungins A−C (**1**−**3**) (Scheme 1), were first isolated by Harris et al. in 1993 from a broth of *Trichederma viride Pers.*[1] These natural products are composed of a polar, structurally unusual, vinyl citrate headgroup derivatized as an amide with phenylalanine or another amino acid and a nonpolar side chain. They were shown to inhibit serine palmitoyl transferase at the nanomolar level as well as inhibiting squalene synthase in vitro at the micromolar level and are thus potent antifungal agents.[2,3] In addition these compounds inhibit Ras-farnesyl transferase and are thus of potential interest as anticancer agents.[4] The viridiofungins, therefore, represent interesting synthetic targets due to both the challenging nature of the highly functionalized citrate core and their application as drug hit structures.

The constitution of viridiofungin A was determined by Harris and co-workers using NMR and mass spectrum data of the natural compound and derived degradation products.[1] The absolute stereochemistry of viridiofungin A (**1**) was assigned to be (3*S*,4*S*,2′*S*) by Hatakeyama and co-workers in 1998 through a 27-step enantioselective total synthesis of the corresponding trimethyl ester in which a Sharpless asymmetric epoxidation was used to set absolute stereochemistry.[5] Subsequently in 2004 and 2005, Hiersemann and co-workers reported diastereoselective 17-step syntheses of triester derivatives of viridiofungin A, A_2, and A_4, which showcased an elegant ester dienolate [2,3] Wittig rearrangement to control the required relative stereochemistry of the branched citrate unit. Subsequent elaboration, coupling to (*S*)-tyrosine, and HPLC separation of diastereoisomers gave the naturally occurring (3*S*,4*S*,2′*S*) triesters and their (3*R*,4*R*,2′*S*) isomers.[6,7] Recently, Hatakeyama noted that the attempted deprotection of synthetic viridiofungin A trimethyl ester resulted in its decomposition. He additionally reported a new 22-step enantioselective total synthesis of viridiofungin A (**1**), which successfully used *tert*-butyl ester protection.[8] Hatakeyama's second synthesis also relied on Sharpless asymmetric epoxidation but differed from the first synthesis in that the lipophilic side chain was added to the vinyl

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(1) Harris, G. H.; Jones, E. T. T.; Meinz, M. S.; Nallin-Omstead, M.; Helms, G. L.; Bills, G. F.; Zink, D.; Wilson, K. E. *Tetrahedron Lett.* **1993**, *34*, 5235.
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(3) Mandala, S. M.; Thornton, R. A.; Frommer, B. R.; Dreikorn, S.; Kurtz, M. B. *J. Antibiot.* **1997**, *50*, 339.
(4) Huang, L.; Lingham, R. B.; Harris, G. H.; Singh, S. B.; Dufresne, C.; Nallin-Omstead, M.; Bills, G. F.; Mojena, M.; Sanchez, M.; et al. *Can. J. Bot.* **1995**, *73*, S898.
(5) Esumi, T.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Tetrahedron Lett.* **1998**, *39*, 877.
(6) Pollex, A.; Abraham, L.; Müller, J.; Hiersemann, M. *Tetrahedron Lett.* **2004**, *45*, 6915.
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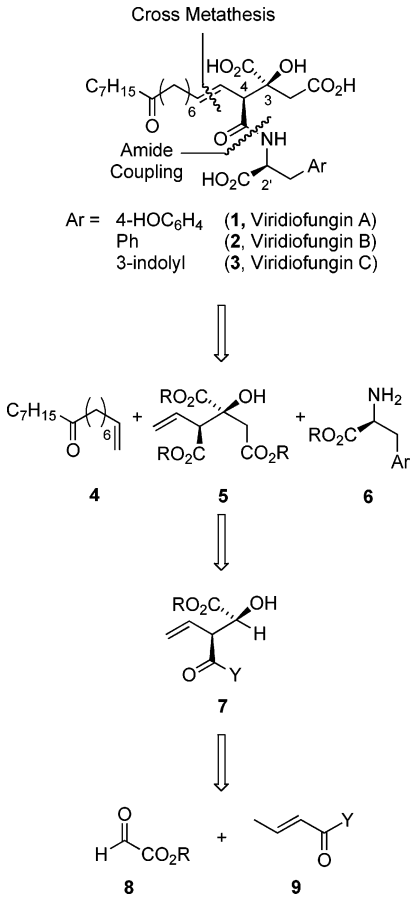
SCHEME 1. Proposed Retrosynthesis



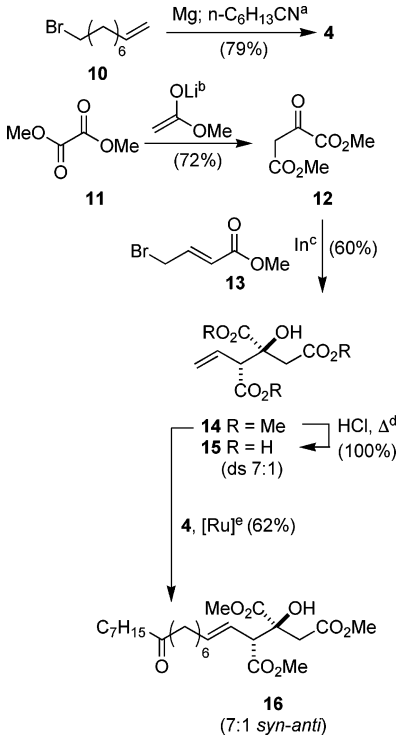
citrate headgroup by using alkene cross-metathesis catalyzed by either the Grubbs' second generation catalyst or the Hoveyda's catalyst.[9,10]

In an effort to develop a shorter, more flexible route to these medicinally interesting compounds, we sought to develop a concise enantioselective and diastereoselective route to the vinyl citrate headgroup **5** and to use alkene cross-metathesis to link the lypophilic side chain **4** (Scheme 1). We considered that the vinyl citrate unit **5**, itself a structurally unusual intermediate with other possible applications in synthesis, should be available from the diastereoselective C-3 alkylation of the vinyl malic acid derivative **7**. In turn, we proposed that an asymmetric aldol reaction between glyoxylic ester **8** and crotonic acid derivative **9** should provide the key intermediate **7**.

Results and Discussion

Coupling of the Grignard reagent prepared from bromide **10** with heptanenitrile gave the target ketone **4** (79%). In an effort to model the key cross-metathesis reaction of alkene **4** with a vinyl citrate, ester **14** was synthesized in a concise manner (Scheme 2), using an indium-mediated crotonylation of ketodiester **12**, which proceeded in good yield albeit with a diastereoselectivity (ds 7:1) that was opposite to that desired for the viridiofungins. The stereochemistry of adduct **14** was

SCHEME 2. Model Metathesis Reaction and Precursor Synthesis[a]



[a] Reagents and conditions: (a) Mg, Et_2O, reflux; *n*-$C_6H_{13}CN$, Et_2O, 25 °C; 1 M HCl (aq), 0 °C. (b) MeOAc, LiN(*i*-Pr)$_2$, THF, −78 °C; MeO_2CCO_2Me, −78 to 25 °C. (c) **13**, In, THF−H_2O (1:1), 25 °C. (d) 1 M HCl (aq), reflux. (e) Grubbs II (**17**) (20 mol %), PhMe, 80 °C.

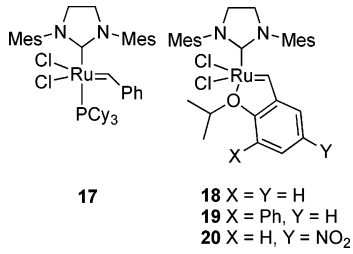


FIGURE 1. Catalysts for cross-metathesis reactions.

assigned by hydrolysis to the known triacid **15**.[11] Attempted cross-metathesis of triester **14** (ds 7:1) with alkene **4** by using the Grubbs-II catalyst (**17**) in dichloromethane at reflux was unsuccessful. However, reaction in toluene at 80 °C gave alkene **16** (62%) as the trans isomer.With this encouraging result, we embarked on an enantioselective synthesis of the required vinyl citrate compounds **5** (Scheme 3). Despite a report by Iseki and co-workers that ethyl glyoxylate participated with poor selectivity in an Evans' aldol reaction,[12] we decided to examine a dibutylboron triflate mediated coupling between this commercially available aldehyde and the Evans' crotonate **21**, which was synthesized according to literature procedures.[13] Pleasingly, the major product (72%) isolated from this reaction was the *syn*-aldol **22**. The relative stereochemistry of imide **22** was

(9) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204. Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749.

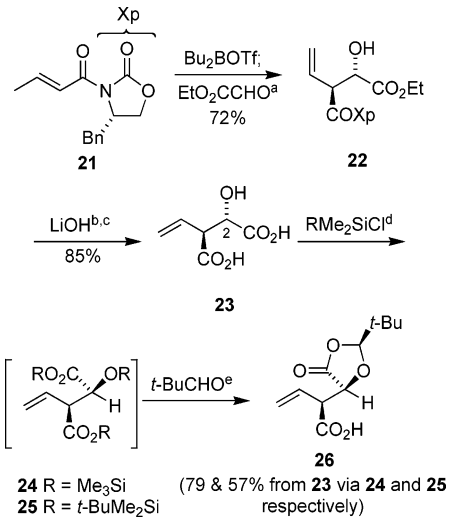
(10) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.

(11) Dolle, R. E.; Novelli, R.; Saxty, B. A.; Wells, T. N. C.; Kruse, L. I.; Camilleri, P.; Eggleston, D. *Tetrahedron Lett.* **1991**, *32*, 4587.

(12) Iseki, K.; Oishi, S.; Kobayashi, Y. *Tetrahedron* **1996**, *52*, 71.

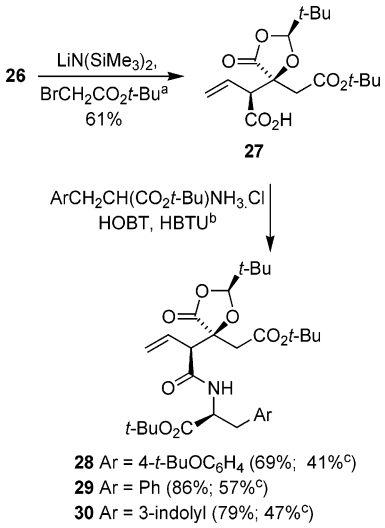
(13) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

SCHEME 3. Synthesis of (2*S*,3*S*) Vinyl Malic Acid[a]



[a] Reagents and conditions: (a) Bu_2BOTf, NEt_3, CH_2Cl_2, −78 to 0 °C; EtO_2CCHO (1.3 equiv), −78 to 0 °C. (b) LiOH, H_2O_2, THF:H_2O (3:1), 0 °C. (c) LiOH, MeOH:H_2O (1:1), 0 to 25 °C. (d) Me_3SiCl or *t*-$BuMe_2SiCl$, *i*-Pr_2NEt, THF, 25 °C. (e) *t*-BuCHO, Me_3SiOTf (20 mol %), CH_2Cl_2, −35 °C.

SCHEME 4. Alkylation of Acid 26 and Amide Coupling of Citrate 27[a]



[a] Reagents and conditions: (a) 1 M $LiN(SiMe_3)_2$ in THF, DMF, −70 °C, 50 min; $BrCH_2CO_2t$-Bu, −70 °C, 15 min. (b) $ArCH_2CH(CO_2t\text{-Bu})NH_3Cl$, HOBT, HBTU, *i*-$Pr_2NEt$, DMF, 0 °C. (c) Second yields refer to overall yields from **26** without purification of the intermediate **27**.

assigned on the basis of an X-ray crystallographic structure determination. Since the oxazolidinone precursor **21** was of known absolute stereochemistry, this study also established the absolute stereochemistry of the aldol unit. Subsequent cleavage of the imide moiety and saponification of the ethyl ester gave vinyl malic acid **23** in good yield (61%) over three steps.

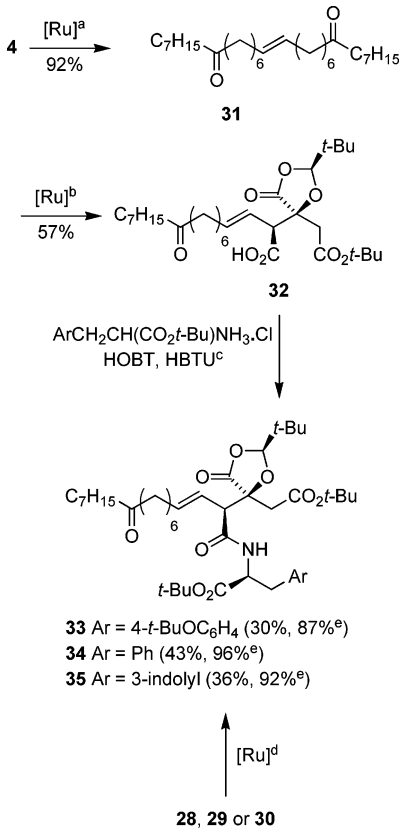
We considered that C-2 alkylation of diacid **23** with retention of stereochemistry should be possible via conversion into dioxolanone **26**, using the Seebach "Self-Reproduction of Stereochemistry" approach (Scheme 3).[14] Due to difficulties in the purification of acid **23**, we attempted to prepare dioxolanone **26** using crude diacid **23**. Following the Hoye protocol,[15] crude acid **23** was converted into the air and moisture-sensitive silyl ester **24** and subsequently condensed with pivaldehyde to stereoselectively provide acetal **26** (79% over 2 steps). In an effort to improve the reaction, we examined the conversion of crude diacid **23** into acetal **26** via *tert*-butyldimethysilyl ester **25**. Unfortunately the yield of this modified process was inferior (57%) and chromatography was required to isolate dioxolanone **26**. In contrast, protection via silyl ester **24** was more convenient in that most of the product dioxolanone **26** was isolated by recrystallization of the crude material.

Conversion of acetal **26** into the vinyl citrate derivative **27** was carried out by deprotonation with lithium hexamethylsilazide in THF at −78 to −30 °C and reaction with *tert*-butyl bromoacetate (Scheme 4). These conditions, which were developed by Seebach for the corresponding malic acid derivative,[14] gave the required acetal **27** but only in poor yield (22%), albeit as a single diastereoisomer and with no starting material recovered. When deprotonation was carried out at lower temperatures in THF no conversion of starting material **26** was observed. When enolization and alkylation were carried out in DMF and THF (5:2) as solvent at −70 °C the reaction was significantly improved and gave acetal **27** (61%) again as a single diastereoisomer. Amide coupling between citrate **27** and H-Tyr(*t*-Bu)-O*t*-Bu, H-Phe-O*t*-Bu, and H-Try-O*t*-Bu mediated by HBTU and HOBT[16] gave the vinyl citrate amides **28** (69%), **29** (86%), and **28** (79%), respectively, all as single diastereoisomers. Furthermore, these amide coupling reactions were also carried out on the crude C-alkylation product **27** thereby circumventing its purification, which was tedious, and providing the vinyl citrate amides **28** (41% from **26**), **29** (57% from **26**), and **28** (47% from **26**) in superior overall yields. The structure and stereochemistry of amide **29** was confirmed by an X-ray crystallographic structure determination and, by reference to the known stereochemistry of the amino acid entity, the absolute stereochemistry was confirmed to be correct for the viridiofungins.

Attempted cross-metathesis reactions between acid **27** and alkene **4** in the presence of the Grubbs II catalyst (**17**) at room temperature or at 50 °C were unsuccessful. The course of reaction was conveniently monitored by ^1H NMR spectroscopy and this indicated that, while acid **27** remained unchanged, complete cross-metathesis of alkene **4** alone giving both alkene **31** and presumably ethylene took place. Unfortunately, unlike the model synthesis of alkene **16** described earlier, attempted cross-metathesis of acid **27** and alkene **4** at 80 °C in toluene proceeded but with very poor conversion. Again the major product formed was alkene **31**. No cross-metathesis of alkene **27** alone was observed. These results indicate that, under Grubbs' classification of alkenes for cross-metathesis, alkene **4** is type I (rapid homodimerization) while citrate **27** is type III (no homodimerization)[17] suggesting the major pathway of any successful reaction will be secondary cross-metathesis between citrate **27** and alkene **31** and thus alkene **4** was duly homodimerized by using carbene **17** in a separate step to save catalyst turnover in this crucial reaction. We therefore sought to closely

(14) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313.
(15) Hoye, T. R.; Peterson, B. H.; Miller, J. D. *J. Org. Chem.* **1987**, *52*, 1351.
(16) HOBT = 1-hydroxy-1,2,3-benzotriazole; HBTU = 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate. See: Dourtoglou, V.; Ziegler, J. C.; Gross, B. *Tetrahedron Lett.* **1978**, 1269.
(17) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

SCHEME 5. Cross-Metathesis of Acid 27 and Amides 28, 29, and 30 and Synthesis of Amides 33, 34, and 35[a]

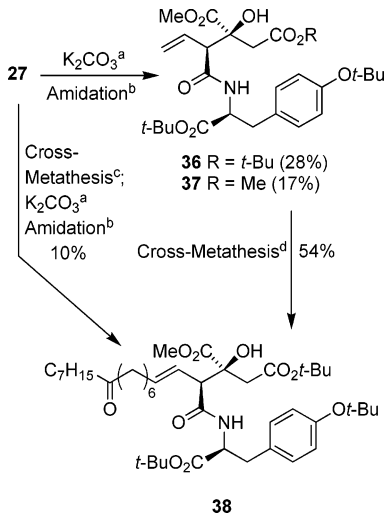


[a] Reagents and conditions: (a) **17** (10 mol %), CH_2Cl_2, 25 °C; (b) **27**, **20** (20 mol %), CH_2Cl_2, 55 °C (microwaves), 1 h. (c) Amino acid HCl salt, HOBT, HBTU, *i*-Pr_2NEt, DMF, 0 °C. (d) **31**, **20** (20 mol %), CH_2Cl_2, 65 °C (microwaves), 4 h. (e) The first yields refer to cross-metathesis of **27** with **31** followed by amide formation; the second yields refer to cross-metathesis from **28**−**30** only.

examine the cross-metathesis of alkene **31** and citrate **27** with variation of temperature, concentration, solvent, and catalyst (Scheme 5). In particular we focused on the use of the Grubbs II catalyst (**17**), the Hoveyda catalyst (**18**),[10] the Blechert catalyst (**19**)[18] and the Grela catalyst (**20**).[19] In our hands, neither catalyst **17** nor **18** was especially effective with slow and incomplete conversions. Both catalysts **19** and **20** were superior with the Grela catalyst **20** the most effective. Although conversion by ^{1}H NMR was high (>95%), extensive chromatography was required to remove ruthenium residues from the polar acid **32**, which was isolated in 57% yield. Microwave heating was employed for operational convenience although conventional heating gave comparable results. The product **32** was isolated as the pure trans isomer as judged by ^{1}H and ^{13}C NMR (J = 15.5 Hz). This material was converted without purification to the viridiofungins A, B, and C derivatives **33**, **34**, and **35**, respectively (30−46% over 2 steps from **27**), and as single diastereoisomers. Alternatively, amides **28**, **29**, and **30** could be converted in high yield (87−92%) into the viridiofungin derivatives **33**, **34**, and **35**, respectively, by cross-metathesis with alkene **31**.

Further confirmation of the correct stereochemical outcome of this synthesis was provided by conversion of intermediate **27** to an alternative protected triester species for comparison

SCHEME 6. Synthesis of Ester 38[a]



[a] Reagents and conditions: (a) K_2CO_3, MeOH, 0 to 25 °C. (b) H-Tyr-(O*t*-Bu)-O*t*-Bu·HCl, HOBT, HBTU, *i*-Pr_2NEt, DMF, 0 °C. (c) **31**, **20** (20 mol %), CH_2Cl_2, 65 °C (microwaves). (d) **31**, **20** (20 mol %), CH_2Cl_2, 55 °C (microwaves).

with data reported by Hatakeyama and Hiersemann (Scheme 6).[5−7] Unfortunately, direct transesterification of amides **33**, **34**, and **35** under either acidic or basic conditions resulted in extensive decomposition. This is in keeping with the observations of Hatakeyama that viridiofungin derivatives are highly sensitive and unstable under standard hydrolysis conditions.[8] Since it has been proposed that this instability is due to retro-aldol processes, we considered that acid **27** would be protected from such degradation under basic conditions by deprotonation to give the carboxylate salt. Consistent with this analysis, transesterification of acid **27** in basic methanol gave rise to the corresponding methyl ester. Most conveniently, this was directly converted into the amide **36**, which greatly simplified purification. Surprisingly dimethyl ester **37** was also isolated from this sequence presumably through an unusual direct base-mediated transesterification of the *tert*-butyl ester. The stereochemistry of triester **36** was confirmed to have the desired (2*S*,3*S*) structure by an X-ray crystallographic structure determination. Finally cross-metathesis of triester **36** with alkene **31** gave the viridiofungin A derivative **38** (54%). The same derivative **38** was also prepared directly from dioxolanone **27** and without isolation of any intermediates by sequential cross-metathesis with alkene **31**, base-catalyzed methanolysis, and peptide coupling. Comparison of ^{1}H and ^{13}C NMR spectra reported for ester **38** by Hatakeyama and Hiersemann[5−8] for the corresponding trialkyl esters of viridiofungin A was consistent with the stereochemical identity of the product.

Conclusion

During these studies we have developed rapid highly stereoselective syntheses of the vinyl malic acid derivative **26** (48% over 4 steps) and the vinyl citric acid derivative **27** (29% over 5 steps) both as single enantiomers, with fully differentiated carboxylate functionality. The vinyl citrate **27** was converted into the viridiofungin derivatives **33**, **34**, **35**, and **38** by using highly convergent, 3-step sequences. The synthetic brevity and

(18) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403.

(19) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318.

overall yields of these syntheses (8 steps from the starting imide **21**, 3−26%) compare favorably with the published procedures of Hatakeyama (2.2% over 27 steps,[5] 7.5% over 22 steps[8]) and Hiersemann (<4% over 18 steps).[6,7] Additionally, there is considerable flexibility in the final three steps with the possibility of easy variation of electrophile, amide coupling partner, and cross-metathesis partner from intermediate acid **26**. Both intermediates **26** and **27** should find use in the synthesis of other unusual citrate natural products.

Experimental Section

(4*S*)-Benzyl-3-(((2*S*,3*S*)-1-ethoxy-2-hydroxy-1-oxo-4-penten-3-yl)carbonyl)-1,3-oxazolidin-2-one (22). *n*-Bu_2BOTf (1.0 M in CH_2Cl_2, 77.0 mL, 77.0 mmol) and NEt_3 (12.6 mL, 90.3 mmol) were added with stirring to imide **21** (17.9 g, 70.0 mmol) in CH_2Cl_2 (350 mL) at −78 °C. After 1 h at −78 °C and 15 min at 0 °C, the resultant yellow solution was cooled to −78 °C and freshly distilled ethyl glyoxalate (2.6 mL, 26 mmol) was added. The reaction mixture was stirred for a further 1 h at −78 °C and 1 h at 0 °C at which time it was poured onto aqueous HCl (1 M; 400 mL), the phases separated, and the aqueous phase extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were washed with H_2O (400 mL) and brine (400 mL), dried ($MgSO_4$), and rotary evaporated. Chromatography (gradient elution 1:2 Et_2O:hexane to 1:1 Et_2O:hexane to 2:1 Et_2O:hexane) gave imide **22** (17.4 g, 72%) as a white crystalline solid: mp 84 °C (Et_2O); $[\alpha]^{25}_D$ + 23.7 (*c* 1.00, $CDCl_3$); IR (film) 1784, 1743, 1693, 1636 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 3H), 7.18 (d, J = 7.0 Hz, 2H), 6.05 (*app*-dt, J = 17.5, 9.5 Hz, 1H), 5.35 (m, 2H), 4.89 (dd, J = 9.0, 5.0 Hz, 1H), 4.71 (m, 1H), 4.59 (d, J = 5.0 Hz, 1H), 4.24 (m, 4H), 3.29 (br s, 1H), 3.25 (dd, J = 13.5, 3.0 Hz, 1H), 2.76 (dd, J = 13.5, 3.0 Hz, 1H), 1.29 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 171.1, 152.9, 134.8, 130.6, 129.3, 128.8, 127.2, 121.1, 70.9, 66.0, 62.0, 55.1, 51.4, 37.4, 14.0; MS (CI, NH_3) *m*/*z* 365 $(M + NH_4)^+$, 348 $(M + H)^+$; HRMS (CI, NH_3) calcd for $C_{18}H_{22}NO_6$ $(M + H)^+$ 348.1447, found 348.1444. Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.02; H, 5.95; N, 3.95.

(2*S*,3*S*)-2-Hydroxy-3-(hydroxycarbonyl)-4-pentenoic Acid (23).[11] H_2O_2 (50 wt %, 9.2 mL, 150 mmol) and $LiOH·H_2O$ (4.2 g, 100 mmol) were added with stirring to the aldol product **22** (17.3 g, 50 mmol) in THF and H_2O (3:1; 250 mL) at 0 °C. After 2 h, H_2O (100 mL) was added followed by $NaHCO_3$ (21.0 g, 250 mmol) and Na_2SO_3 (25.2 g, 200 mmol) and the THF rotary evaporated. The aqueous residue was extracted with CH_2Cl_2 (2 × 250 mL) and the combined organic extracts were extracted with H_2O (60 mL). The combined aqueous extracts were saturated with solid NaCl and carefully acidified to pH 1 with concentrated aqueous HCl and the acidified aqueous phase was extracted with EtOAc (4 × 600 mL). The combined EtOAc extracts were dried ($MgSO_4$) and rotary evaporated to give crude ethyl (2*S*,3*S*)-2-hydroxy-3-(hydroxycarbonyl)-4-pentenoate (8.0 g, 85%) as a colorless oil: $[\alpha]^{25}_D$ −32.0 (*c* 1.00, $CDCl_3$); IR (film) 3454, 1733, 1644 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.99 (*app*-dt, J = 17.5, 10.0 Hz, 1H), 5.32 (d, J = 10.0 Hz, 1H), 5.23 (d, J = 17.5 Hz, 1H), 4.74 (d, J = 3.5 Hz, 1H), 4.27 (m, 2H), 3.55 (dd, J = 9.5, 3.5 Hz, 1H), 1.31 (t, J = 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 172.3, 129.6, 121.2, 71.5, 62.4, 53.2, 14.2; MS (CI, NH_3) *m*/*z* 206 $(M + NH_4)^+$; HRMS (CI, NH_3) calcd for $C_8H_{16}NO_5$ $(M + NH_4)^+$ 206.1028, found 206.1033. The crude ester was used directly without further purification. $LiOH·H_2O$ (5.4 g, 129 mmol) was added to the crude ethyl ester (8.0 g, 43 mmol) in MeOH and H_2O (1:1; 200 mL) at 0 °C and this mixture was stirred overnight at room temperature. After rotary evaporation of MeOH, the aqueous residue was extracted with CH_2Cl_2 (2 × 100 mL), and the organic phases were combined and back extracted with H_2O (50 mL). The combined aqueous phases were saturated with NaCl, acidified to pH 1 with concentrated aqueous HCl, and extracted with CH_2Cl_2 (2 × 100 mL) and EtOAc (4 × 500 mL). The CH_2Cl_2 extracts were discarded. The combined EtOAc extracts were dried ($MgSO_4$) and rotary evaporated to give crude diacid **23** (7.2 g, ca. 100%) as a colorless oil. Solid-phase extraction of a small portion of crude material with CH_2Cl_2 at reflux left a white powder, which was recrystallized from MeCN and $CHCl_3$ to give diacid **23** as a white crystalline solid: mp 111−116 °C (MeCN−$CHCl_3$); $[\alpha]^{25}_D$ −9.8 (*c* 1.00, MeOH); IR (film) 3304, 1758, 1690 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 6.00 (*app*-dt, J = 18.0, 9.5 Hz, 1H), 5.16 (m, 2H), 4.68 (d, J = 3.5 Hz, 1H), 3.47 (dd, J = 3.5, 9.5 Hz, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ 174.5, 173.5, 133.0, 120.5, 73.1, 54.6; MS (CI, NH_3) *m*/*z* 178 $(M + NH_4)^+$; HRMS (CI, NH_3) *m*/*z* calcd for $C_6H_{12}NO_5$ $(M + NH_4)^+$ 178.0715, found 178.0715. Anal. Calcd for $C_6H_8O_5$: C, 45.01; H, 5.04. Found: C, 44.90; H, 4.90.

(*S*)-2-((2*S*,4*S*)-2-*tert*-Butyl-5-oxo-1,3-dioxolan-4-yl)-3-butenoic Acid (26). All manipulations were carried out under Ar. Me_3SiCl (3.8 mL, 30 mmol) followed by *i*-Pr_2NEt (5.2 mL, 30 mmol) were added to acid **23** (1.6 g, 10 mmol) in THF (50 mL). After 2 h, hexane (50 mL) was added and the mixture was cooled to −78 °C. This suspension was filtered, the residue was extracted with hexane (20 mL), and the combined filtrates were rotary evaporated to give a pale yellow oil. This was treated with hexane (20 mL) at −14 °C and refiltered to remove residual salts. The residue was extracted with a further portion of hexane (5 mL) and the combined filtrates were rotary evaporated to give the crude trisilyl derivative **24** (3.1 g, 82%) as a pale yellow oil. This material was dissolved in CH_2Cl_2 (40 mL) at −35 °C, *t*-BuCHO (0.93 mL, 8.3 mmol) and Me_3SiOTf (0.30 mL, 1.7 mmol) were added sequentially, and the mixture was stirred for 16 h at −35 °C. From this point onward manipulations were performed in air. The mixture was poured into aqueous HCl (1 M; 40 mL), stirred for a further 10 min at room temperature, and extracted with Et_2O:hexane (1:1; 100 mL). The combined organic extracts were washed with H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$), and rotary evaporated to give a pale yellow solid. Recrystallization from Et_2O−hexane gave acid **26** (1.6 g, 69%) as a white crystalline solid. Chromatography of the mother liquors (gradient elution hexane to 1:2 Et_2O: hexane to 1:1 Et_2O:hexane) and recrystallization gave a further portion of acid **26** (0.17 g, 9%; combined yield 1.8 g, 79% over two steps). Only one diastereoisomer was observed by ^1H NMR, which was assigned to be syn by NOESY spectroscopy: mp 120−121 °C (Et_2O−hexane); $[\alpha]^{25}_D$ −19.4 (*c* 1.00, $CDCl_3$); IR (film) 3084, 1794, 1701, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.97 (*app*-dt, J = 17.0, 10.5, 9.0 Hz, 1H), 5.36 (d, J = 10.0 Hz, 1H), 5.35 (d, J = 17.0 Hz, 1H), 5.14 (d, J = 1.0 Hz, 1H), 4.74 (dd, J = 4.0, 1.0 Hz, 1H), 3.62 (dd, J = 9.0, 4.0 Hz, 1H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 171.0, 128.6, 122.3, 109.6, 75.6, 50.4, 34.4, 23.6; MS (CI, NH_3) *m*/*z* 246 $(M + NH_4)^+$, 229 $(M + H)^+$; HRMS (CI, NH_3) *m*/*z* calcd for $C_{11}H_{20}NO_5$ 246.1341 $(M + NH_4)^+$, found 246.1336. Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.77; H, 6.92.

(*S*)-2-((2*S*,4*S*)-4-*tert*-Butyloxycarbonylmethyl-2-*tert*-butyl-5-oxo-1,3-dioxolan-4-yl)-3-butenoic Acid (27). $LiN(SiMe_3)_2$ in THF (1.0 M; 1.00 mL, 1.00 mmol) was added dropwise with stirring over 1 min to dioxalone **26** (228 mg, 1.00 mmol) in DMF (5.0 mL) at −70 °C. The solution was stirred for 1 min after addition was completed at which time additional $LiN(SiMe_3)_2$ in THF (1.0 M; 1. 0 mL, 1.00 mmol) was added dropwise over 1 min. After 50 min, $BrCH_2CO_2t$-Bu (0.16 mL, 1.0 mmol) was added to the resulting pale orange solution. After a further 15 min, AcOH (1 M in THF; 1.0 mL) was added and the mixture was partitioned between Et_2O and hexane (1:1; 25 mL) and aqueous HCl (25 mL) and the phases were separated. The organic phase was washed with H_2O (25 mL) and brine (25 mL). The combined aqueous layers were extracted with Et_2O and hexane (1:1; 25 mL), and the combined organic extracts were dried ($MgSO_4$) and rotary evaporated. Chromatography (gradient elution hexane to Et_2O:hexane 1:2 to Et_2O:hexane 1:1) gave a white solid, which was recrystallized

from *n*-hexane to give acid **27** (209 mg, 61%) as a white solid: mp 111 °C (hexane); $[\alpha]^{25}_D$ −67.8 (*c* 1.00, $CDCl_3$); R_f 0.16 (1:1 Et_2O:hexane); IR (film) 3414, 1795, 1723, 1632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.12 (*app*-dt, J = 17.0, 10.0 Hz, 1H), 5.42 (m, 2H), 5.26 (s, 1H), 3.70 (d, J = 9.5 Hz, 1H), 3.00 (d, J = 16.0 Hz, 1H), 2.78 (d, J = 16.0 Hz, 1H), 1.46 (s, 9H), 0.96 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.2, 172.5, 168.0, 129.4, 123.0, 109.2, 82.3, 79.7, 56.0, 38.8, 34.3, 27.9, 23.7; MS (CI) *m*/*z* 360 $(M + NH_4)^+$, 304 $(M - t\text{-Bu} + H + NH_4)^+$; HRMS (CI) *m*/*z* calcd for $C_{17}H_{30}NO_7$ $(M + NH_4)^+$ 360.2025, found 360.2022. Anal. Calcd for $C_{17}H_{26}O_7$: C, 59.64; H, 7.65. Found: C, 59.38; H, 7.42.

***tert*-Butyl (*S*)-3-(4-*tert*-Butyloxyphenyl)-2-((*S*)-2-((2*S*,4*S*)-2-*tert*-butyl-4-*tert*-butyloxycarbonylmethyl-5-oxo-1,3-dioxolan-4-yl)but-3-enoylamino)propanoate (28). Method A:** HOBT (50 mg, 0.37 mmol), *i*-Pr_2NEt (0.13 mL, 0.73 mmol), H-Tyr(*t*-Bu)-O*t*-Bu·HCl (122 mg, 0.37 mmol), and HBTU (140 mg, 0.37 mmol) were added sequentially to citrate **27** (104 mg, 0.30 mmol) in DMF (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, partitioned between Et_2O and hexane (1:1; 25 mL) and aqueous HCl (1 M; 25 mL), the phases separated, and the organic layer washed sequentially with H_2O (25 mL), saturated aqueous $NaHCO_3$ (25 mL), H_2O (25 mL), and brine (25 mL). The aqueous extracts were combined and back extracted with Et_2O and hexane (1:1; 100 mL) and the combined organic phases were dried ($MgSO_4$), rotary evaporated, and chromatographed (gradient elution 5:1 EtOAc:hexane to 4:1 EtOAc:hexane) to give amide **28** (128 mg, 69%) as a pale yellow viscous oil: $[\alpha]^{25}_D$ −28.2 (*c* 1.00, $CDCl_3$); R_f 0.37 (1:3 EtOAc:hexane); IR (film) 3409, 3365, 1798, 1729, 1663, 1567 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.03 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 6.45 (d, J = 7.5 Hz, 1H), 6.06 (ddd, J = 18.0, 13.5, 9.0 Hz, 1H), 5.30 (m, 2H), 5.24 (s, 1H), 4.69 (dt, J = 7.5, 6.0 Hz, 1H), 3.42 (d, J = 9.5 Hz, 1H), 3.05 (dd, J = 14.0, 5.5 Hz, 1H), 2.97 (d, J = 16.0 Hz, 1H), 2.76 (d, J = 16.0 Hz, 1H), 1.45 (s, 9H), 1.38 (s, 9H), 1.31 (s, 9H), 0.95 (s, 9H); ^{13}C ($CDCl_3$, 100 MHz) δ 172.6, 170.2, 168.3, 167.9, 154.2, 131.2, 130.8, 130.0, 124.0, 121.8, 109.7, 82.3, 82.2, 80.4, 78.3, 57.6, 53.6, 39.4, 37.3, 34.3, 28.7, 27.9, 23.9; MS (CI) *m*/*z* 635 $(M + NH_4)^+$, 618 $(M + H)^+$; HRMS (CI) *m*/*z* calcd for $C_{34}H_{52}NO_9$ $(M + H)^+$ 618.3642, found 618.3641. Anal. Calcd for $C_{34}H_{51}NO_9$: C, 66.10; H, 8.32; N, 2.27. Found: C, 65.97; H, 8.06; N, 2.19.

(*S*)-2-((*S*)-4-*tert*-Butyloxycarbonylmethyl-2-*tert*-butyl-5-oxo-1,3-dioxolan-4-yl)-11-oxooctadec-3*E*-enoic Acid (32). Dioxolanone **27** (72 mg, 0.20 mmol), dione **31** (45 mg, 0.10 mmol), and carbene **20** (28 mg, 0.020 mmol, 20 mol %) were dissolved in freeze−thaw degassed CH_2Cl_2 (0.20 mL) under Ar and the resultant mixture microwave heated at 65 °C for 4 h. Rotary evaporation and chromatography (gradient elution hexane to 1:2 Et_2O:hexane to 1:1 Et_2O:hexane) gave alkene **32** (63 mg, 57%) as a pale yellow oil: $[\alpha]^{25}_D$ −42.6 (*c* 1.00, $CDCl_3$); R_f 0.27 (1:1 Et_2O:hexane); IR (film) 3209, 1801, 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (dt, J = 15.5, 6.5 Hz, 1H), 5.71 (dd, J = 15.5, 9.0 Hz, 1H), 5.24 (s, 1H), 3.63 (d, J = 9.0 Hz, 1H), 2.96 (d, J = 15.8 Hz, 1H), 2.75 (d, J = 16.0 Hz, 1H), 2.38 (t, J = 7.5 Hz, 4H), 2.06 (*app*-dd, J = 13.5, 6.5 Hz, 2H), 1.55 (m, 4H), 1.46 (s, 9H), 1.26 (m, 14H), 0.95 (s, 9H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 174.5, 172.0, 168.1, 139.5, 120.9, 109.0, 82.2, 79.8, 55.2, 42.8, 42.7, 38.9, 34.2, 32.4, 31.6, 29.6, 29.2, 28.9, 28.8, 28.5, 27.9, 23.8, 23.7, 23.5, 22.5, 14.0; MS (CI, NH_3) *m*/*z* 570 $(M + NH_4)^+$; HRMS (CI) *m*/*z* calcd for $C_{31}H_{56}NO_8$ $(M + NH_4)^+$ 570.4006, found 570.4015. Anal. Calcd for $C_{31}H_{52}O_8$: C, 67.36; H, 9.48. Found: C, 67.25; H, 9.35.

***tert*-Butyl (*S*)-3-(4-*tert*-Butyloxyphenyl)-2-((*S*)-2-((2*S*,4*S*)-2-*tert*-butyl-4-*tert*-butyloxycarbonylmethyl-5-oxo-1,3-dioxolan-4-yl)-11-oxooctadec-3*E*-enoylamino)propanoate (33). Method A:** Carbene **20** (34 mg, 0.050 mmol, 20 mol %) was added to dione **31** (56 mg, 0.13 mmol) and amide **28** (153 mg, 0.25 mmol) in freeze−thaw degassed CH_2Cl_2 (0.25 mL) (Ar). The mixture was microwave heated at 65 °C for 4 h, rotary evaporated, and chromatographed (gradient elution 1:5 EtOAc:hexane to 1:4 EtOAc:hexane) to give amide **33** (179 mg, 87%) as a pale yellow oil: $[\alpha]^{25}_D$ −47.8 (*c* 1.00, $CDCl_3$); R_f 0.38 (1:3 EtOAc:hexane); IR (film) 3412, 3358, 1798, 1730, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 6.46 (d, J = 7.5 Hz, 1H), 5.67 (m, 2H), 5.23 (s, 1H), 4.68 (dt, J = 13.5, 7.5 Hz, 1H), 3.35 (d, J = 8.5 Hz, 1H), 3.02 (m, 2H), 2.94 (d, J = 16.0 Hz, 1H), 2.75 (d, J = 16.0 Hz, 1H), 2.37 (t, J = 7.5 Hz, 4H), 2.02 (m, 2H), 1.54 (br s, 4H), 1.44 (s, 9H), 1.37 (s, 9H), 1.31 (s, 9H), 1.26 (br s, 14H), 0.95 (s, 9H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 172.1, 170.2, 168.6, 168.4, 154.2, 138.3, 130.9, 130.0, 123.9, 122.6, 109.0, 82.2, 82.1, 80.7, 78.2, 56.8, 53.6, 42.8, 42.7, 39.6, 37.4, 34.2, 32.5, 31.6, 29.2, 29.0, 28.7, 27.9, 23.9, 23.8, 23.7, 22.5, 14.0; MS (FAB) *m*/*z* 828 $(M + H)^+$; HRMS (FAB) *m*/*z* calcd for $C_{48}H_{78}NO_{10}$ $(M + H)^+$ 828.5626, found 828.5637.

***tert*-Butyl (3*S*,4*S*)-4-((1*S*)-1-*tert*-Butyloxycarbonyl)-2-(*tert*-butyloxycarbonylphenyl)ethylaminocarbonyl)-3-hydroxy-3-(methoxycarbonyl)-5-hexenoate (36).** Solid K_2CO_3 (130 mg, 1.0 mmol) was added with stirring to dioxolanone **27** (34 mg, 0.10 mmol) in MeOH (1.0 mL) and the resultant mixture was stirred for 18 h at room temperature. The mixture was partitioned between EtOAc (25 mL) and aqueous HCl (1 M; 25 mL) and the phases were separated. The aqueous phase was saturated with NaCl and extracted with EtOAc (5 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and rotary evaporated and the residue was taken up in DMF (0.5 mL) and cooled to 0 °C, and HOBT (16 mg, 0.12 mmol), H-Tyr(O*t*-Bu)-*t*-Bu·HCl (38 mg, 0.12 mmol), *i*-Pr_2NEt (45 μL, 0.24 mmol), and HBTU (44 mg, 0.12 mmol) were added. This mixture was stirred for 90 min at 0 °C and subsequently 30 min at room temperature after which time it was partitioned between Et_2O and hexane (1:1; 25 mL) and aqueous HCl (1M; 25 mL). The phases were separated and the organic phase was washed with H_2O (25 mL), saturated aqueous $NaHCO_3$ (25 mL), H_2O (25 mL), and brine (25 mL). The combined aqueous washings were extracted with Et_2O and hexane (1:1; 25 mL) and the combined organic extracts dried ($MgSO_4$) and rotary evaporated. Chromatography (1:2 EtOAc:hexane) gave diester **36** (16 mg, 28%) as a white crystalline solid and diester **37** (8.8 mg, 17%) as a colorless oil. Diester **36**: mp 117−119 °C (Et_2O−hexane); $[\alpha]^{25}_D$ −7.9 (*c* 1.00, $CDCl_3$); R_f 0.20 (1:3 EtOAc:hexane); IR (film) 3473, 3356, 1734, 1659, 1609 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.0 Hz, 2H), 6.78 (d, J = 7.5 Hz, 1H), 5.90 (*app*-dt, J = 17.0, 10.0 Hz, 1H), 5.22 (d, J = 10.5 Hz, 1H), 5.22 (d, J = 17.0 Hz, 1H), 4.70 (*app*-q, J = 6.0 Hz, 1H), 4.47 (s, 1H), 3.77 (s, 3H), 3.18 (d, J = 9.5 Hz, 1H), 3.04 (d, J = 6.0 Hz, 2H), 2.85 (d, J = 16.0 Hz, 1H), 2.63 (d, J = 16.0 Hz, 1H), 1.43 (s, 9H), 1.38 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 170.2, 169.4, 169.1, 154.2, 131.4, 130.9, 130.0, 124.1, 120.9, 82.2, 81.6, 78.3, 76.6, 59.0, 53.7, 52.9, 43.0, 37.4, 28.8, 27.9; MS (CI, NH_3) *m*/*z* 564 $(M + H)^+$, 508 $(M - t\text{-Bu} + H)^+$; HRMS (CI) *m*/*z* calcd for $C_{30}H_{46}NO_9$ $(M + H)^+$ 564.3173, found 564.3186. Anal. Calcd for $C_{30}H_{45}NO_9$: C, 63.92; H, 8.05; N, 2.48. Found: C, 63.87; H, 7.95; N, 2.40. Diester **37**: $[\alpha]^{25}_D$ −4.0 (*c* 1.00, $CDCl_3$); R_f 0.10 (1:3 EtOAc:hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.77 (d, J = 8.0 Hz, 1H), 5.91 (m, 1H), 5.24 (d, J = 9.8 Hz, 1H), 5.23 (d, J = 16.4 Hz, 1H), 4.69 (*app*-dt, J = 8.0, 6.5 Hz, 1H), 4.54 (s, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.21 (d, J = 9.5 Hz, 1H), 3.07 (dd, J = 14.0, 6.0 Hz, 1H), 3.01 (dd, J = 14.0, 6.5 Hz, 1H), 2.89 (d, J = 16.0 Hz, 1H), 2.66 (d, J = 16.0 Hz, 1H), 1.39 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 170.5; 170.2, 169.5, 154.3, 131.2, 130.9, 129.9, 124.1, 121.2, 82.3, 78.3, 76.5, 58.8, 53.7, 53.1, 51.9, 41.5, 37.2, 28.7, 27.9; MS (CI, NH_3) *m*/*z* 539 $(M + NH_4)^+$, 523 $(M + H)^+$, 522 $(M)^+$; HRMS (CI) *m*/*z* calcd for $C_{27}H_{40}NO_9$ $(M + H)^+$ 522.2703, found 522.2720. Anal. Calcd for $C_{27}H_{39}NO_9$: C, 62.17; H, 7.54; N, 2.69. Found: C, 62.16; H, 7.59; N, 2.67.

***tert*-Butyl (3*S*,4*S*)-4-((1*S*)-1-*tert*-Butyloxycarbonyl)-2-(*tert*-butyloxycarbonylphenyl)ethylaminocarbonyl)-3-hydroxy-3-(methoxycarbonyl)-13-oxo-5*E*-eicosenoate (38). Method A:** Dioxolanone **27** (34 mg, 0.10 mmol), dione **31** (22 mg, 0.050 mmol), and

carbene **20** (13 mg, 0.020 mmol, 20 mol %) were dissolved in freeze−thaw degassed CH_2Cl_2 (0.10 mL) under Ar and the resultant mixture microwave heated at 55 °C for 1 h. The solvent was rotary evaporated, the residue was dissolved in MeOH (1.0 mL), K_2CO_3 (130 mg, 1.0 mmol) was added, and the resulting mixture was stirred for 18 h at room temperature. The mixture was partitioned between EtOAc (25 mL) and aqueous HCl (1 M; 25 mL) and the phases separated. The aqueous phase was saturated with NaCl and extracted with EtOAc (5 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and rotary evaporated and the residue was dissolved in DMF (0.5 mL) and cooled to 0 °C and HOBT (16 mg, 0.12 mmol), H-Tyr(O*t*-Bu)-*t*-Bu·HCl (38 mg, 0.12 mmol), *i*-Pr_2NEt (45 μL, 0.24 mmol), and HBTU (44 mg, 0.12 mmol) were added. The mixture was stirred for 90 min at 0 °C and subsequently at 30 min at room temperature after which time it was partitioned between Et_2O and hexane (1:1; 25 mL) and aqueous HCl (1 M; 25 mL). The phases were separated and the organic phase was washed with H_2O (25 mL), saturated aqueous $NaHCO_3$ (25 mL), H_2O (25 mL), and brine (25 mL). The combined aqueous washings were extracted with Et_2O and hexane (1:1; 25 mL) and the combined organic extracts dried ($MgSO_4$) and rotary evaporated. Chromatography (1:3 EtOAc:cyclohexane) gave amide **38** (8.1 mg, 10%) as a pale yellow oil. **Method B:** Ester **36** (15 mg, 0.027 mmol), dione **31** (5.8 mg, 0.014 mmol), and carbene **20** (1.8 mg, 0.0054 mmol, 20 mol %) were dissolved in freeze−thaw degassed CH_2Cl_2 (0.03 mL) under Ar and the resultant mixture was microwave heated at 65 °C for 4 h. The solvent was rotary evaporated and the residue chromatographed (1:2 EtOAc:hexane) to give amide **38** (11 mg, 54%) as a colorless oil: $[\alpha]^{25}_D$ −6.3 (*c* 0.63, $CDCl_3$); R_f 0.25 (1:3 EtOAc:hexane); IR (film) 3426, 3362, 3328, 1733, 1661, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 7.5 Hz, 1H), 5.56 (m, 2H), 4.68 (dd, J = 13.5, 6.0 Hz, 1H), 3.75 (s, 3H), 3.13 (d, J = 9.5 Hz, 1H), 3.06 (dd, J = 13.5, 6.0 Hz, 1H), 3.01 (dd, J = 13.5, 6.0 Hz, 1H), 2.84 (d, J = 16.0 Hz, 1H), 2.62 (d, J = 16.0 Hz, 1H), 2.37 (t, J = 7.5 Hz, 4H), 1.99 (m, 2H), 1.55 (m, 4H), 1.42 (s, 9H), 1.37 (s, 9H), 1.31 (s, 9H), 1.25 (br s, 14H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 173.4, 170.2, 170.1, 169.1, 154.2, 137.5, 137.3, 130.0, 127.0, 124.0, 82.1, 81.5, 78.3, 76.3, 58.0, 53.7, 52.8, 43.1, 42.8, 42.6, 37.4, 31.9, 31.6, 29.6, 29.2, 29.0, 28.8, 27.9, 23.8, 22.5, 14.0; MS (CI, NH_3) *m*/*z* 774 $(M + H)^+$, 718 $(M - t\text{-Bu} + H)^+$; HRMS (CI) *m*/*z* calcd for $C_{44}H_{72}NO_{10}$ $(M + H)^+$ 774.5156, found 774.5164.

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Supporting Information Available: Additional experimental procedures and structural data for all new compounds; crystallographic data (including ORTEPs and CIFs) for compounds **22**, **29**, and **36** (CCDC 606372, 606373, and 606374, respectively); copies of ^1H NMR and ^{13}C NMR spectra for selected new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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