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# Total Synthesis of Citrafungin A

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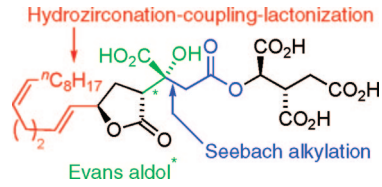


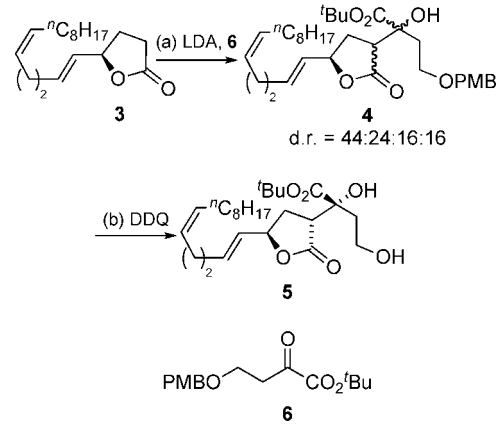

The antifungal natural product citrafungin A was synthesized using, as key steps, an asymmetric aldol reaction of a chiral oxazolidinone, diastereoselective alkylation of a chiral 1,3-dioxolan-2-one, semihydrogenation of an enyne, and selective methyl ester deprotection.

## Introduction

In 2004, the Rahway Merck group reported the isolation and structural determination of two novel alkyl citrate natural products, citrafungin A (**1**) and citrafungin B (**2**) (Figure 1), from the fermentation broth of an Alaskan coprophilous fungus.[1] These compounds are potent inhibitors of fungal geranylgeranyltransferase I (GGTase I) enzymes, which catalyze the transfer of a terpene side chain to a cysteine residue of the proteins Rho1p and Cdc42p, thereby promoting their membrane localization and biological activity. Rho1p is a regulatory subunit of the crucial enzyme 1,3-$\beta$-D-glucan synthase, which is involved in fungal cell wall biosynthesis. Since there are only low levels of homology between fungal and human GGTase I, inhibition of the fungal enzyme is likely to provide novel fungicidal agents of low toxicity. Citrafungin A (**1**) inhibits a range of fungal pathogens including strains of *Candida albicans*, *Candida neoformans* and *Aspergillus fumigatus* with MIC values of 0.4−13 $\mu$M. It is clear from these results that the citrafungins are intriguing hit structures for the development of new classes of antifungal drugs.

The Hatakeyama group recently reported the first total synthesis of citrafungin A (**1**).[2] Having successfully accomplished the total synthesis of (±)-trachyspic acid[3] and thereby determining its relative stereochemistry, they applied the same strategy in their synthesis of citrafungin A (**1**) by using the aldol reaction between α-ketoester **6** and the lithium enolate of lactone **3** as the key step (Scheme 1). This reaction led to a mixture of four diastereoisomers (44:24:16:16), in favor of desired lactone, which were only separable after deprotection of the *p*-methoxybenzyl group. In the late stages of the synthesis, the Japanese group used the Keck esterification[4] to introduce the isocitrate unit.

**SCHEME 1. Key Steps in the Hatakeyama Total Synthesis of Citrafungin A (1)**[a]




3 4 5 6

[a] Reagents and conditions: (a) LDA, THF, HMPA, −78 °C; **6**; (b) DDQ, $CH_2Cl_2$, $H_2O$.

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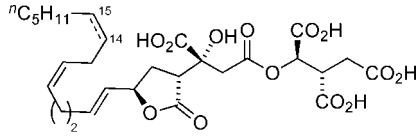
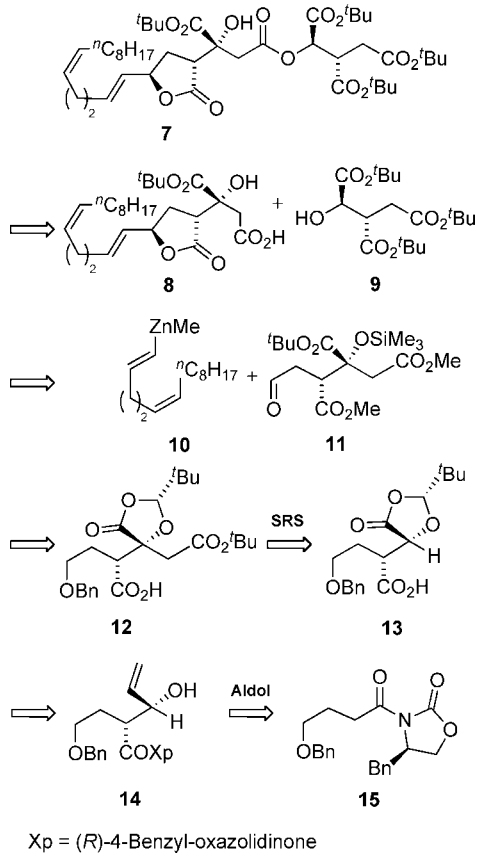


**citrafungin A (1)** (14,15-dihydro)
**citrafungin B (2)** (14,15-*cis*-olefin)

**FIGURE 1.** Structures of citrafungins A and B.

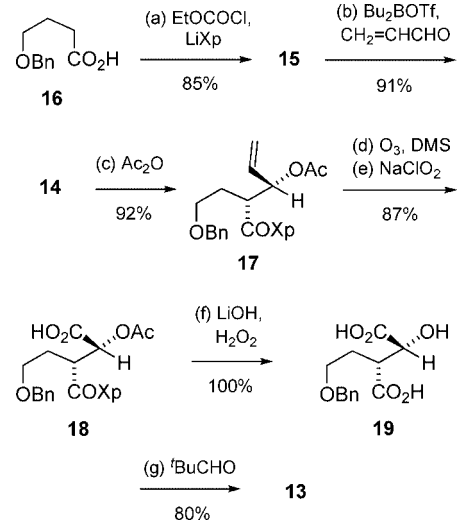
**SCHEME 2. Proposed Retrosynthesis**



Xp = (*R*)-4-Benzyl-oxazolidinone

As part of our studies on alkylcitrate metabolites, we sought to extend our stereoselective synthesis of the viridiofungins[6] to the related citrafungins. The proposed retrosynthesis is shown in Scheme 2. Following the Hatakeyama precedent, citrafungin A (**1**) should be available from the deprotection of tetraester **7** derived from acid **8** and alcohol **9**. In our approach, acid **8** should be available using a late-stage aldehyde **11** and alkenylzinc **10** addition-lactonization reaction. In turn, aldehyde **11** should be available from ether **12**, which should be prepared from dioxolanone **13** using a stereoselective Seebach "Self Reproduction of Stereocenter"[7,8] (SRS) enolate alkylation reaction. The precursor **14** of dioxolanone **13** should be available using an Evans aldol reaction.[9] Herein we report the application of this approach in a stereoselective total synthesis of citrafungin A (**1**).

**SCHEME 3. Synthesis of Dioxolanone 13**[a]



[a] Reagents and Conditions: (a) (i) EtOCOCl, $Et_3N$, $Et_2O$; (ii) *n*-BuLi and (*R*)-4-benzyl-2-oxazolidinone; (b) *n*-$Bu_2BOTf$, $Et_3N$, $CH_2Cl_2$, −78 °C; $CH_2$=CHCHO, $CH_2Cl_2$, −78 to 0 °C; (c) $Ac_2O$, $Et_3N$, 4-DMAP, $Et_2O$; (d) $O_3$, DMS, $CH_2Cl_2$, −78 °C; (e) $NaClO_2$, $NaH_2PO_4$, 2-methyl-2-butene, $^t$BuOH, THF, $H_2O$ (1:1:1); (f) LiOH, $H_2O_2$, THF, $H_2O$ (1:1); (g) $^t$BuCHO, *p*-TsOH, *n*-hexane, THF (10:1).

## Results and Discussion

Commercially available 4-benzyloxybutyric acid **16** was converted into the acyl-oxazolidinone **15** by formation of the mixed anhydride with ethyl chloroformate followed by reaction with (*R*)-4-benzyl-*N*-lithio-2-oxazolidinone at −78 °C (Scheme 3).[9] Evans *syn*-selective aldol reaction using di-*n*-butylboron triflate, triethylamine and propenal gave alcohol **14** in 91% yield with excellent diastereoselectivity (d.r. > 99%). Sequential acetylation, ozonolysis[10] and Pinnick oxidation of hydroxyalkene **14** gave the carboxylic acid **18** in 80% yield over the 3 steps.[11] Dual oxazolidinone and acetate hydrolysis using lithium hydroxide and hydrogen peroxide gave diacid **19**, which was converted into dioxolanone **13** by condensation with excess pivaldehyde catalyzed with *p*-toluenesulfonic acid in 80% yield as a 94:6 mixture in favor of the desired *cis*-isomer, the structure of which was confirmed by $^1$H NOESY NMR.

The alkylation of dioxolanone **13** was carried out by double deprotonation in dry DMF at −70 °C using lithium hexamethyldisilazide followed by alkylation using *t*-butyl bromoacetate in DMF solution (Scheme 4).[6] Whereas this reaction was completely diastereoselective in the case of the viridiofungins, the reaction proceeded with a d.r. > 9:1 with substrate **13**. Selective deprotection of the *t*-butyl ester in **12** was achieved using trifluoroacetic acid in dichloromethane and gave diacid **20** (100%). This partial deprotection was essential to prevent extensive decomposition during the opening of the dioxolanone ring. Dioxolanone **20** was smoothly opened using benzyl alcohol and lithium hexamethyldisilazide in toluene to afford, after diazomethane methylation, ester **21** in 50% yield over the 4 steps. It was found to be crucial to open the dioxolanone at this stage since it enabled differentiation between the carboxyl groups in **21**. Selective debenzylation of the benzyl ester in the presence of the benzyl ether was achieved by hydrogenolysis

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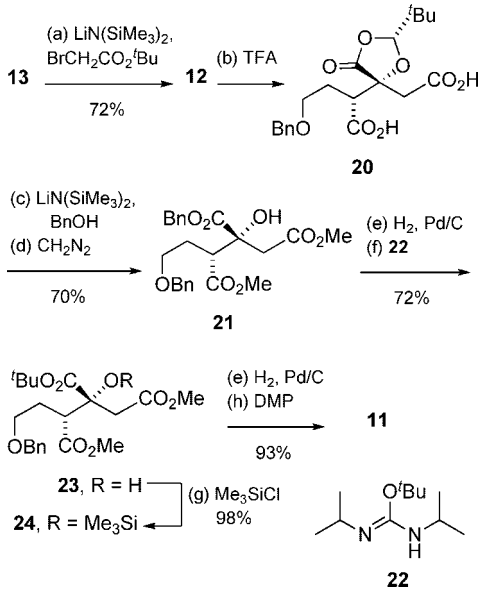
**SCHEME 4. Synthesis of Aldehyde 11**[a]

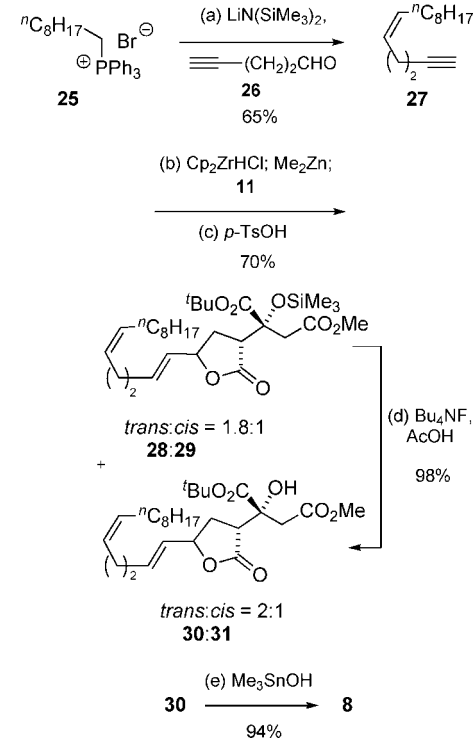



[a] Reagents and Conditions: (a) $LiN(SiMe_3)_2$, $BrCH_2CO_2{}^tBu$, DMF; (b) TFA, $CH_2Cl_2$; (c) BnOH, $LiN(SiMe_3)_2$, PhMe; (d) $CH_2N_2$, EtOAc; (e) $H_2$, Pd/C, THF; (f) **22**, $CH_2Cl_2$; (g) $Me_3SiCl$, imidazole, $CH_2Cl_2$; (h) Dess Martin periodinane, $CH_2Cl_2$.

over palladium on carbon in THF.[12] Reprotection of the free carboxylic acid as the *t*-butyl ester **23** was carried out using freshly prepared *N*,*N*′-di-isopropyl-*O*-*t*-butylisourea (**22**) in 72% yield over the 2 steps.[13] Sequential trimethylsilylation, benzyl ether hydrogenolysis (which was slower than the ester **21** hydrogenolysis) and Dess-Martin oxidation[14] of **23** gave aldehyde **11** which was directly used in the next step.

The citrafungin lipophilic side chain was synthesized using the Wittig reaction[15] of commercially available 1-nonyltriphenylphosphonium bromide **25** and 4-pentynal[16] **26** to afford alkyne **27** as the *cis* isomer in 65% yield (Scheme 5). Alkyne **27** hydrozirconation[17] using the Schwarz reagent followed by transmetalation[18,19] at low temperature with dimethylzinc gave selectively the *trans* organozinc compound **10**, which was directly added at 0 °C to the crude aldehyde **11**. Subsequent acid catalyzed lactonization gave a mixture of the *trans*-**28** and the *cis*-**29** lactones (1.8:1). During chromatography on silica, partial cleavage of the trimethylsilyl group occurred but fortunately the resultant four lactones were separable. Treatment of either lactone **28** or **29** with acetic acid buffered tetrabutylammonium fluoride[20] cleanly gave lactones **30** or **31** respectively in 98% yield. Overall the lactones **30** and **31** were obtained in 70% yield from **24** in with the major isomer having the correct *trans*-stereochemistry (2:1). The stereoselectivity of

**SCHEME 5. Synthesis of Acid 8**[a]




[a] Reagents and Conditions: (a) $LiN(SiMe_3)_2$, 4-pentynal, THF; (b) $Cp_2ZrHCl$, $CH_2Cl_2$, 0−20 °C; $Me_2Zn$, −65 °C; **11**, 0−20 °C; (c) *p*-TsOH, $Et_2O$, reflux; (d) $Bu_4NF$, AcOH, THF; (e) $Me_3SnOH$, $ClCH_2CH_2Cl$, 85 °C.

this reaction could be possibly enhanced using Wipf methodology[18] although such a modification was not investigated. The structures of lactones **30** and **31** were confirmed by $^1H$ NOESY and $^1H-^{13}C$ HMBC NMR experiments.

The final step to obtain acid **8** was the selective deprotection of the methyl ester in presence of a *t*-butyl ester and a delicate lactone susceptible to epimerization. All standard saponification procedures[21−24] were indiscriminate giving mixture of acids. These results may be explained by a neighboring group effect of the tertiary alcohol leading to partial hydrolysis of the adjacent *t*-butyl ester via the α-lactone or *via* the combined inductive effect of the two adjacent carbonyls and hydroxyl groups enhancing the electrophilicity of the *t*-butyl ester. Attempted demethylation using lithium iodide[25] or thiophenol and cesium carbonate[26] were too slow or resulted in partial lactone *trans* to *cis* epimerization respectively. However, selective demethylation was achieved using hydroxytrimethylstannane in 1,2-dichloroethane[27] giving acid **8** in 94% yield.

Following the Hatakeyama precedent, alcohol **9** was prepared[2] from commercially available (*R*)-malic acid **32** via ester **33**, which was alkylated with allyl bromide by double deprotonation (Scheme 6). Sequential acylation, ruthenium oxidation[28] and esterification of **34** gave ester **36** in 72% yield over the 3 steps.

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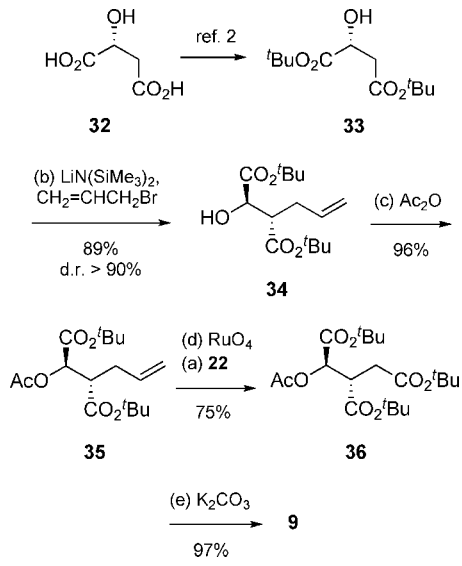
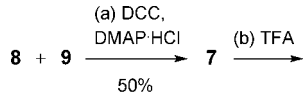
**SCHEME 6. Synthesis of Alcohol 9**[a]




[a] Reagents and Conditions: (a) **22**, $CH_2Cl_2$; (b) $LiN(SiMe_3)_2$, allyl bromide, THF −78 to 0 °C; (c) $Ac_2O$, $Et_3N$, 4-DMAP, $Et_2O$; (d) $RuCl_3$, $NaIO_4$, $CCl_4$, MeCN, $H_2O$ (5:5:8); (e) $K_2CO_3$, MeOH.

**SCHEME 7. Synthesis of Citrafungin A (1)**[a]




[a] Reagents and Conditions: (a) DCC, DMAP·HCl, $CH_2Cl_2$; (b) TFA, $CH_2Cl_2$.

Hydrolysis of the acetate group with potassium carbonate in methanol cleanly provided alcohol **9** in 97% yield. The full experimental procedures for these transformations are provided in this paper, since they are not reported in the prior Hatakeyama work.

Again following the Hatakeyama precedent, esterification of carboxylic acid **8** with alcohol **9** using the Keck's esterification procedure[4] (Scheme 7) gave pentaester **7** in 50% yield. Global deprotection using trifluoroacetic acid quantitatively gave citrafungin A (**1**), which was further purified by HPLC. The sample showed $^1H$ and $^{13}C$ NMR data in excellent agreement with those reported by the Rahway Merck group.[1]

## Conclusion

In summary, we report the total synthesis of citrafungin A using an Evans aldol reaction, Seebach dioxolanone alkylation and introduction of the lipophilic chain *via* an alkyne hydrozirconation-aldehyde addition-lactonization sequence. The methodology developed should be applicable to the synthesis of related natural products such as (−)-trachyspic acid,[29] (*R*,*R*)-CJ-13,981, (*R*,*R*)-CJ-13,982,[30] (*R*,*R*)-agaric acid and their enantiomers.

## Experimental Section

**(*R*)-4-Benzyl-3-[2-((*R*)-2-benzyloxyethyl)-(*S*)-3-hydroxy-4-pentenoyl]-oxazolidin-2-one (14).** *n*-$Bu_2BOTf$ in $CH_2Cl_2$ (1 M; 100 mL, 100 mmol) and $Et_3N$ (15 mL, 50.6 mmol) were added with stirring to oxazolidinone **15** (31.5 g, 89.2 mmol) in $CH_2Cl_2$ (600 mL) at −78 °C. After 1 h at −78 °C and 1 h at 0 °C, the mixture was cooled to −78 °C and freshly distilled $CH_2$═CHCHO (7.8 mL, 116 mmol) was added with stirring. After 1 h at −78 °C and 1 h at 0 °C, the mixture was poured onto aqueous HCl (1 M; 600 mL), the phases were separated and the aqueous phase extracted with $CH_2Cl_2$ (2 × 200 mL). The combined organic layers were washed with brine (500 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (hexanes/EtOAc 4:1) gave alcohol **14** (33.2 g, 91%) as a viscous oil: $R_f$ 0.30 (hexanes: $Et_2O$ 6: 1); $[\alpha]_D^{25}$ −29 (*c* 1.0, $CHCl_3$); IR (KBr) 3488, 1778, 1695, 1386, 1351, 1205, 1101, 1018, 738, 700 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.33−7.24 (m, 8H), 7.12−7.10 (m, 2H), 5.88 (m, 1H), 5.33 (dt, $J$ = 17.2, 1.4 Hz, 1H), 5.21 (dt, $J$ = 10.6, 1.3 Hz, 1H), 4.60−4.54 (m, 1H), 4.46 (d, $J$ = 2.6 Hz, 2H), 4.44−4.39 (m, 1H), 4.26 (m, 1H), 4.10 (t, $J$ = 8.4 Hz, 1H), 4.04 (dd, $J$ = 9.0, 2.7 Hz, 1H), 3.60 (dd, $J$ = 5.4, 1.5 Hz, 1H), 3.59 (d, $J$ = 5.3 Hz, 1H), 3.16 (dd, $J$ = 13.4, 3.2 Hz, 1H), 2.81 (d, $J$ = 3.1 Hz, 2H), 2.27−2.17 (m, 1H), 2.09 (dd, $J$ = 13.4, 10.5 Hz, 1H), 2.00−1.93 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 175.0, 153.6, 138.1, 137.3, 135.7, 129.3, 128.8, 128.4, 128.2, 127.7, 127.1, 116.7, 73.6, 73.3, 68.9, 66.0, 55.7, 46.2, 37.2, 28.0; MS (CI) *m*/*z* 410 $(M + H)^+$, 427 $(M + NH_4)^+$; HRMS (ESI) calcd for $C_{24}H_{28}NO_5$: $(M + H)^+$, 410.1967, found: $(M + H)^+$, 410.1973.

**(*R*)-2-Acetoxy-(*R*)-3-((*R*)-4-benzyl-2-oxo-oxazolidine-3-carbonyl)-5-benzyloxy-pentanoic acid (18).** Acetate **17** (33 g, 73.2 mmol) in $CH_2Cl_2$ (20 mL) was cooled to −78 °C and a stream of ozone was bubbled through the mixture until a deep-blue color persisted. Oxygen was then bubbled through the solution for an additional 20 min to remove excess of ozone. $Me_2S$ (25 mL, 366 mmol) was added at −78 °C, and the solution was allowed to warm to room temperature. Rotary evaporation gave the crude aldehyde, which was directly oxidized. Solid $NaH_2PO_4$ (44 g, 366 mmol) and $NaClO_2$ (26.5 g, 293 mmol) were added sequentially with stirring to aldehyde and 2-methyl-2-butene (116 mL, 1.1 mol) in *t*-BuOH, $H_2O$, THF (1:1:1; 600 mL) at 0 °C. The mixture was allowed to warm to room temperature overnight and quenched by the addition of saturated aqueous $Na_2SO_3$ (600 mL) and saturated aqueous $NH_4Cl$ (200 mL). The mixture was acidified to pH 1 using aqueous HCl (concd), saturated with NaCl and extracted with EtOAc (2 × 500 mL). The combined organic layers were washed with brine (500 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (gradient hexanes/EtOAc 1:1; EtOAc/MeOH 4:1 to 7:3) gave carboxylic acid **18** (30 g, 63.8 mmol, 87%) as a colorless oil: $R_f$ 0.32 (MeOH: $CH_2Cl_2$ 1: 4); $[\alpha]_D^{25}$ −59.5 (*c* 1.0, MeOH); IR (KBr) 1778, 1751, 1700, 1388, 1213, 1105, 1074, 744, 700 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.32−7.22 (m, 8H), 7.12−7.10 (m, 2H), 5.55 (d, $J$ = 5.4 Hz, 1H), 4.66−4.46 (m, 2H), 4.52 (d, $J$ = 11.8 Hz, 1H), 4.45 (d, $J$ = 11.8 Hz, 1H), 4.16 (t, $J$ = 8.4 Hz, 1H), 4.04 (dd, $J$ = 9.1, 2.8 Hz, 1H), 3.65−3.54 (m, 2H), 3.14 (dd, $J$ = 13.4, 3.2 Hz, 1H), 2.38−2.28 (m, 1H), 2.22 (dd, $J$ = 13.3, 10.4 Hz, 1H), 2.13 (s, 3H), 2.07−1.99 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 171.8, 171.5, 169.9, 153.3, 137.8, 135.3, 129.3, 128.8, 128.4, 128.0, 127.7, 127.1, 73.1, 71.2, 67.9, 66.3, 55.6, 42.3, 37.3, 28.0, 20.5; HRMS (ESI) calcd for $C_{25}H_{28}NO_8$: $(M + H)^+$, 470.1815, found: $(M + H)^+$, 470.1817; Anal. calcd for $C_{25}H_{27}NO_8$: C, 63.96; H, 5.80; N, 2.98. Found: C, 63.92; H, 5.70; N, 2.91.

**4-Benzyloxy-(*R*)-2-((*R*)-2-*tert*-butyl-(*R*)-5-oxo-[1,3]dioxolan-4-yl)-butyric acid (13).** *p*-TsOH (3.9 g, 20.5 mmol) and *t*-BuCHO (22.6 mL, 205.8 mmol) were added with stirring to carboxylic acid **19** (18.4 g, 68.6 mmol) in *n*-hexane and THF (10:1; 500 mL), and the mixture was stirred under reflux for 5 h with azeotropic removal of water (Dean−Stark). The mixture was cooled to room temperature and poured onto aqueous HCl (1 M; 400 mL). The organic layer was washed with brine (500 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography ($CH_2Cl_2$/MeOH 40:1) gave dioxolanone **13** (18.4 g, 54.8 mmol, 80%) as a white solid: $R_f$ 0.30

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($CH_2Cl_2$/MeOH 20:1); mp 105−110 °C (hexanes/$CH_2Cl_2$); $[\alpha]_D^{25}$ +10.2 (*c* 1.0, $CHCl_3$); IR (KBr) 1799, 1714, 1484, 1409, 1195, 1091, 971, 736, 698 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.30 (m, 5H), 5.14 (d, $J$ = 1.0 Hz, 1H), 4.69 (dd, $J$ = 3.9, 1.1 Hz, 1H), 4.57 (d, $J$ = 11.8 Hz, 1H), 4.53 (d, $J$ = 11.8 Hz, 1H), 3.69−3.64 (m, 1H), 3.16 (dt, $J$ = 8.8, 3.9 Hz, 1H), 2.24−2.15 (m, 1H), 1.95−1.88 (m, 1H), 0.98 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 176.5, 171.6, 137.7, 128.4, 127.74, 127.71, 109.4, 75.1, 73.0, 67.5, 43.3, 34.2, 27.1, 23.5; HRMS (ESI) calcd for $C_{18}H_{23}O_6$: $(M - H)^+$, 335.1495, found: $(M - H)^+$, 335.1506; Anal. calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.37; H, 7.23.

**4-Benzyloxy-(*R*)-2-(4-*tert*-butoxycarbonylmethyl-2-(*R*)-*tert*-butyl-(*R*)-5-oxo-[1,3]dioxolan-4-yl)-butyric acid (12).** $LiN(SiMe_3)_2$ in THF (1 M; 1 mL, 1 mmol) was added dropwise to acid **13** (168 mg, 0.5 mmol) in dry DMF (1 mL) and the resulting pale yellow solution stirred at −70 °C for 50 min, when *t*-butyl bromoacetate (82 $\mu$L, 0.5 mmol) was added. The reaction temperature was maintained at −70 °C for 15 min after which time the solution was poured onto aqueous HCl (1 M; 10 mL) and $Et_2O$ (30 mL) was added. The organic phase was washed with brine (3 × 20 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography ($CH_2Cl_2$/MeOH 40:1)) gave carboxylic acid **12** (165 mg, 0.37 mmol, 73%), a yellow gum, as a mixture of diastereoisomers (9:1): $R_f$ 0.32 ($CH_2Cl_2$/MeOH 20:1); IR (KBr) 1800, 1730, 1366, 1244, 1192, 1155, 1097 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.34−7.26 (m, 5H), 5.28 (s, 1H), 4.50 (d, $J$ = 12.0 Hz, 1H), 4.46 (d, $J$ = 12.0 Hz, 1H), 3.58−3.45 (m, 2H), 3.16 (d, $J$ = 16.5 Hz, 1H), 3.10 (dd, $J$ = 11.3, 2.6 Hz, 1H), 2.84 (d, $J$ = 16.5 Hz, 1H), 2.20−2.12 (m, 1H), 2.05−1.97 (m, 1H), 1.45 (s, 9H), 0.95 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 175.8, 172.5, 168.6, 138.0, 128.2, 127.5, 127.5, 109.7, 82.3, 79.6, 72.9, 67.5, 49.4, 38.8, 34.4, 27.9, 23.6; HRMS (ESI) calcd for $C_{24}H_{34}NaO_8$: $(M + Na)^+$, 473.2151, found: $(M + Na)^+$, 473.2157.

**Benzyl 5-Benzyloxy-(*R*)-2-hydroxy-(*R*)-3-methoxycarbonyl-(*R*)-2-methoxycarbonylmethyl-pentanoate (21).** *t*-Butyl ester **12** (165 mg, 0.37 mmol) in $CH_2Cl_2$ (5 mL) was treated at 0 °C with trifluoroacetic acid (1 mL). The mixture was stirred for 4 h at room temperature and toluene was added (10 mL) and solvent rotary evaporated to give crude diacid **20** (144 mg, 0.37 mmol, 100%) as a yellow gum, which was dissolved in dry PhMe (15 mL) and cooled at 0 °C. Benzyl alcohol (303 $\mu$L, 3 mmol) was added followed by slow addition of $LiN(SiMe_3)_2$ in THF (1 M; 1.85 mL, 1.87 mmol), and the mixture was stirred at room temperature. After 12 h, the solution was poured onto saturated aqueous $NaHCO_3$ (20 mL), the aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic layers were discarded. The aqueous layer was slowly acidified with concentrated hydrochloric acid to pH 1 and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (2 × 50 mL), dried ($MgSO_4$) and freshly prepared diazomethane (solution in $Et_2O$) was added until the yellow coloration persisted. Rotary evaporation followed by chromatography (hexanes/$Et_2O$ 3:2) gave benzyl ester **21** (111 mg, 0.26 mmol, 70%) as a pale yellow oil: $R_f$ 0.25 ($Et_2O$/hexanes 1:1); $[\alpha]_D^{25}$ −0.3 (*c* 1.0, $CH_2Cl_2$); IR (KBr) 1737, 1436, 1357, 1195, 1172, 1099, 738, 698 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.36−7.26 (m, 10H), 5.22 (q, $J$ = 12.1 Hz, 2H), 4.42 (dd, $J$ = 15.2, 11.9 Hz, 2H), 3.96 (*br*s, 1H), 3.60 (s, 3H), 3.51 (s, 3H), 3.48−3.35 (m, 2H), 3.13 (d, $J$ = 16.5 Hz, 1H), 2.95 (dd, $J$ = 11.5, 2.7 Hz, 1H), 2.73 (d, $J$ = 16.5 Hz, 1H), 2.15−2.06 (m, 1H), 1.86−1.78 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 173.3, 172.3, 170.9, 138.1, 134.8, 128.6, 128.5, 128.2, 127.6, 127.5, 75.7, 72.8, 68.1, 67.9, 51.9, 51.8, 50.8, 40.6, 27.4; HRMS (ESI) calcd for $C_{24}H_{29}O_8$: $(M + H)^+$, 445.1862, found: $(M + H)^+$, 445.1862.

***tert*-Butyl 5-Benzyloxy-(*R*)-2-hydroxy-(*R*)-3-methoxycarbonyl-(*R*)-2-methoxycarbonylmethyl-pentanoate (23).** Powdered Pd/C (10%, 300 mg) was added to benzyl ester **21** (390 mg, 0.88 mmol) in dry THF (15 mL) under $H_2$ pressure. The mixture was magnetically stirred for 1 h, filtered through Celite while being rinsed with $Et_2O$ and rotary evaporated to give crude carboxylic acid (310 mg, 87 mmol, 100%) as a colorless oil. This crude acid (310 mg, 0.87 mmol) in $CH_2Cl_2$ (15 mL) was allowed to react with *N*,*N*′-di-isopropyl-*O*-*t*-butylisourea **(22)** (2 mL, excess) and the mixture stirred under reflux for 12 h. Rotary evaporation and chromatography (hexanes: $Et_2O$ 1: 1) gave *t*-butyl ester **23** (260 mg, 0.63 mmol, 72%) as a colorless oil: $R_f$ 0.30 ($Et_2O$/hexanes 1:1); $[\alpha]_D^{25}$ −1.1 (*c* 1.0, $CH_2Cl_2$); IR (KBr) 1741, 1436, 1369, 1157, 1103, 669 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.25 (m, 5H), 4.45 (dd, $J$ = 15.6, 12.0 Hz, 2H), 3.87 (*br*s, 1H), 3.66 (s, 3H), 3.63 (s, 3H), 3.51−3.45 (m, 1H), 3.43−3.38 (m, 1H), 3.07 (d, $J$ = 16.2 Hz, 1H), 2.90 (dd, $J$ = 11.6, 2.6 Hz, 1H), 2.71 (d, $J$ = 16.2 Hz, 1H), 2.17−2.08 (m, 1H), 1.90−1.82 (m, 1H), 1.49 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 172.5, 172.4, 170.7, 138.2, 128.2, 127.6, 127.5, 83.6, 75.2, 72.8, 68.1, 51.8, 51.7, 51.1, 40.7, 27.7, 27.6; HRMS (ESI) calcd for $C_{21}H_{30}NaO_8$: $(M + Na)^+$, 433.1838, found: $(M + Na)^+$, 433.1841.

***tert*-Butyl (*R*)-3-methoxycarbonyl-(*R*)-2-methoxycarbonylmethyl-5-oxo-(*R*)-2-trimethylsilanyloxy-pentanoate (11).** Powdered Pd/C (10%, 300 mg) was added to benzyl ether **24** (270 mg, 0.56 mmol) in dry THF (20 mL) under $H_2$ pressure and the mixture was stirred for 15 h, filtered through Celite while being rinsed with $Et_2O$, and rotary evaporated to give the crude alcohol (219 mg, 0.56 mmol, 100%) as a colorless oil. This alcohol (219 mg, 0.56 mmol) in $CH_2Cl_2$ (20 mL) was allowed to react with Dess-Martin-periodinane (356 mg, 0.84 mmol) at 0 °C. After 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL) and saturated aqueous $Na_2SO_3$ (15 mL) and the mixture stirred for 30 min. The organic layer was dried ($MgSO_4$) and rotary evaporated to give the crude aldehyde **11** (204 mg, 0.52 mmol, 93%) as a colorless oil: $R_f$ 0.40 ($Et_2O$/hexanes 1:2); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.75 (s, 1H), 3.70 (s, 3H), 3.65 (s, 3H), 3.30 (dd, $J$ = 10.9, 2.9 Hz, 1H), 3.09 (dd, $J$ = 18.5, 11.3 Hz, 1H), 3.01 (d, $J$ = 15.5 Hz, 1H), 2.79 (d, $J$ = 15.5 Hz, 1H), 2.65 (dd, $J$ = 18.5, 2.9 Hz, 1H), 1.47 (s, 9H), 0.13 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 199.4, 171.3, 170.5, 170.0, 82.9, 78.3, 52.0, 51.5, 47.6, 42.5, 42.2, 27.7, 2.3; HRMS (ESI) calcd for $C_{17}H_{30}NaO_8Si$: $(M + Na)^+$, 413.1608, found: $(M + Na)^+$, 413.1590.

**1-*tert*-Butyl 4-methyl (*R*)-2-((*R*)-2-oxo-5-tetradeca-1,5-dienyl-tetrahydro-furan-(*R*)-3-yl)-(*R*)-2-trimethylsilanyloxy-succinate (28).** Alkyne **27** (160 mg, 0.83 mmol) in $CH_2Cl_2$ (2 mL) was added dropwise with stirring to $Cp_2ZrHCl$ (180 mg, 0.76 mmol) in $CH_2Cl_2$ (2 mL) at 0 °C. The mixture was stirred at room temperature until a homogeneous solution was formed and subsequently cooled to −65 °C. $Me_2Zn$ in PhMe (1.2 M; 0.55 mL, 0.76 mmol) was added over 5 min after which time the mixture was warmed to 0 °C and aldehyde **11** (200 mg, 0.51 mmol) in $CH_2Cl_2$ (2 mL) was added over 10 min. The reaction mixture was stirred at room temperature for 12 h and poured onto aqueous HCl (1 M; 20 mL). $Et_2O$ (30 mL) was added and the layers were separated. The organic layer was washed with brine (30 mL), dried ($MgSO_4$) and *p*-TsOH (200 mg, excess) was added with stirring. After 3 h at reflux, rotary evaporation and chromatography (gradient hexanes/$Et_2O$ 6:1 to 4:1 to 2:1) gave in order of increasing polarity (1) silyl protected *trans*-lactone **28** (95 mg, 0.17 mmol, 34%) as a pale-yellow oil; (2) silyl protected *cis*-lactone **29** (55 mg, 0.10 mmol, 19%) as a colorless oil; (3) *trans*-lactone **30** (33 mg, 0.07 mmol, 14%) as a colorless oil; (4) *cis*-lactone **31** (10 mg, 0.02 mmol, 4%) as a colorless oil.

**28:** $R_f$ 0.40 ($Et_2O$/hexanes 1:5); $[\alpha]_D^{25}$ +9.8 (*c* 0.8, $CH_2Cl_2$); IR (KBr) 1770, 1747, 1436, 1369, 1249, 1186, 1153, 1070, 1002, 844, 757, 686 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.76 (dt, $J$ = 15.0, 6.2 Hz, 1H), 5.48−5.29 (m, 3H), 4.87 (q, $J$ = 7.2 Hz, 1H), 3.67 (s, 3H), 3.27−3.18 (m, 3H), 2.40 (ddd, $J$ = 13.1, 7.6, 5.3 Hz, 1H), 2.11 (*br*m, 4H), 2.04−1.98 (m, 3H), 1.47 (s, 9H), 1.27 (*br*s, 12H), 0.88 (t, $J$ = 6.8 Hz, 3H), 0.15 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 175.4, 170.5, 170.2, 134.7, 130.9, 128.4, 128.2, 82.6, 79.5, 79.3, 51.6, 47.4, 41.8, 32.2, 31.9, 31.2, 29.6, 29.5, 29.3, 27.8, 27.3, 26.5, 22.7, 14.1, 2.2; HRMS (ESI) calcd for $C_{30}H_{53}O_7Si$: $(M + H)^+$, 553.3561, found: $(M + H)^+$, 553.3561; Anal. calcd for $C_{30}H_{52}O_7Si$: C, 65.18; H, 9.48. Found: C, 65.25; H, 9.39.

**29:** $R_f$ 0.30 ($Et_2O$/hexanes 1:5); $[\alpha]_D^{25}$ +36.7 (*c* 0.8, $CH_2Cl_2$); IR (KBr) 1774, 1745, 1436, 1369, 1249, 1176, 1157, 1072, 1006, 844, 755, 688 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.81 (dt, $J$ = 15.0, 6.2 Hz, 1H), 5.50−5.30 (m, 3H), 4.68 (dt, $J$ = 9.87, 6.99 Hz, 1H), 3.67 (s, 3H), 3.40 (d, $J$ = 15.4 Hz, 1H), 3.32 (dd, $J$ = 11.4, 8.9 Hz, 1H), 3.29 (d, $J$ = 15.4 Hz, 1H), 2.26 (ddd, $J$ = 12.8, 8.9, 6.5 Hz, 1H), 2.12 (*br*m, 5H), 2.01 (dd, $J$ = 6.9, 6.8 Hz, 2H), 1.47 (s, 9H), 1.26 (*br*s, 12H), 0.88 (t, $J$ = 6.8 Hz, 3H), 0.15 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 174.5, 170.6, 170.3, 135.5, 130.8, 128.2, 127.9, 82.5, 78.2, 77.7, 51.5, 47.6, 41.2, 32.2, 31.8, 30.9, 29.6, 29.5, 29.3, 27.8, 27.2, 26.4, 22.6, 14.0, 2.1; HRMS (ESI) calcd for $C_{30}H_{53}O_7Si$: $(M + H)^+$, 553.3561, found: $(M + H)^+$, 553.3568; Anal. calcd for $C_{30}H_{52}O_7Si$: C, 65.18; H, 9.48. Found: C, 65.18; H, 9.55.

**30:** $R_f$ 0.32 ($Et_2O$/hexanes 1:2); $[\alpha]_D^{25}$ −18.5 (*c* 0.6, $CH_2Cl_2$); IR (KBr) 3482, 1768, 1743, 1438, 1269, 1282, 1253, 1189, 1155, 1122, 993, 971, 844 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.79 (dt, $J$ = 14.6, 6.1 Hz, 1H), 5.45−5.28 (m, 3H), 4.98 (q, $J$ = 7.1 Hz, 1H), 3.99 (*br*s, 1H), 3.68 (s, 3H), 3.57 (d, $J$ = 16.6 Hz, 1H), 2.93 (d, $J$ = 16.6 Hz, 1H), 2.86 (dd, $J$ = 9.8, 5.4, 1H), 2.33 (ddd, $J$ = 13.0, 7.4, 5.4 Hz, 1H), 2.11 (*br*m, 4H), 2.02−1.93 (m, 3H), 1.49 (s, 9H), 1.26 (*br*s, 12H), 0.88 (t, $J$ = 6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 175.0, 172.0, 171.1, 135.0, 130.9, 128.1, 127.9, 83.7, 79.6, 75.5, 51.8, 46.2, 40.5, 32.1, 31.8, 30.5, 29.6, 29.4, 29.2, 27.7, 27.2, 26.4, 22.6, 14.1; HRMS (ESI) calcd for $C_{27}H_{44}O_7Na$: $(M + Na)^+$, 503.2985, found: $(M + Na)^+$, 503.2991; Anal. calcd for $C_{27}H_{44}O_7$: C, 67.47; H, 9.23. Found: C, 67.47; H, 9.19.

**31:** $R_f$ 0.30 ($Et_2O$/hexanes 1:2); $[\alpha]_D^{25}$ +11.6 (*c* 0.5, $CH_2Cl_2$); IR (KBr) 3480, 1773, 1743, 1438, 1369, 1284, 1252, 1156, 995, 844 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.82 (dt, $J$ = 15.2, 6.5 Hz, 1H), 5.55−5.30 (m, 3H), 4.71 (dt, $J$ = 9.7, 7.0 Hz, 1H), 3.97 (*br*s, 1H), 3.77 (d, $J$ = 16.5 Hz, 1H), 3.68 (s, 3H), 2.95 (dd, $J$ = 11.5, 8.7 Hz, 1H), 2.89 (d, $J$ = 16.5 Hz, 1H), 2.18 (ddd, $J$ = 12.7, 8.8, 6.2 Hz, 1H), 2.12−2.06 (m, 5H), 1.99 (q, $J$ = 6.9 Hz, 2H), 1.50 (s, 9H), 1.26 (*br*s, 12H), 0.88 (t, $J$ = 6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 174.2, 171.9, 171.0, 136.1, 130.9, 128.1, 127.4, 83.7, 78.7, 74.0, 51.7, 46.9, 40.1, 32.1, 31.8, 30.3, 29.6, 29.4, 29.2, 27.7, 27.2, 26.3, 22.6, 14.1; HRMS (ESI) calcd for $C_{27}H_{44}O_7Na$: $(M + Na)^+$, 503.2985, found: $(M + Na)^+$, 503.2981; Anal. calcd for $C_{27}H_{44}O_7$: C, 67.47; H, 9.23. Found: C, 67.51; H, 9.27.

***tert*-Butyl (*R*)-2-hydroxy-(*R*)-2-((*R*)-2-oxo-5-tetradeca-1,5-dienyl-tetrahydro-furan-(*R*)-3-yl)-succinate (8).** Solid $Me_3SnOH$ (213 mg, 1.17 mmol) was added to methyl ester **30** (113 mg, 0.23 mmol) in $ClCH_2CH_2Cl$ (5 mL) and heated at 85 °C in a sealed tube for 12 h. After rotary evaporation, the crude product was dissolved in EtOAc (20 mL) and washed with aqueous HCl (1 M; 2 × 20 mL) and brine (20 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography ($CH_2Cl_2$/MeOH 15:1) gave carboxylic acid **8** (103 mg, 0.22 mmol, 94%) as a pale-yellow gum: $R_f$ 0.30 ($CH_2Cl_2$/MeOH 15:1); $[\alpha]_D^{25}$ −9.9 (*c* 1.0, $CH_2Cl_2$); IR (KBr) 3452, 1728, 1435, 1399, 1370, 1275, 1251, 1191, 1155, 1119, 999, 969, 840 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.79 (dt, $J$ = 15.2, 6.1 Hz, 1H), 5.47−5.30 (m, 3H), 4.99 (dd, $J$ = 14.0, 7.00 Hz, 1H), 3.97 (*br*s, 1H), 3.58 (d, $J$ = 16.8 Hz, 1H), 2.99 (d, $J$ = 16.8 Hz, 1H), 2.88 (dd, $J$ = 9.8, 5.6 Hz, 1H), 2.33 (ddd, $J$ = 13.1, 7.4, 5.6 Hz, 1H), 2.11 (*br*m, 4H), 2.02−1.94 (m, 3H), 1.48 (s, 9H), 1.26 (*br*s, 12H), 0.88 (t, $J$ = 6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 175.1, 174.5, 171.7, 135.2, 130.9, 128.1, 127.8, 84.1, 79.8, 75.3, 46.2, 40.4, 32.1, 31.8, 30.4, 29.6, 29.4, 29.3, 27.7, 27.2, 26.4, 22.6, 14.1; HRMS (ESI) calcd for $C_{26}H_{42}O_7Na$: $(M + Na)^+$, 489.2828, found: $(M + Na)^+$, 489.2837; Anal. calcd for $C_{26}H_{42}O_7$: C, 66.93; H, 9.07. Found: C, 66.86; H, 8.98.

**Di-*tert*-butyl (*S*)-3-*tert*-Butoxycarbonyl-(*R*)-2-[(*R*)-3-*tert*-butoxycarbonyl-(*R*)-3-hydroxy-(*R*)-3-((*R*)-2-oxo-5-tetradeca-1,5-dienyl-tetrahydro-furan-(*R*)-3-yl)-propanoyloxy]-pentanedioate (7).** DMAP·HCl (66 mg, 0.42 mmol)) and DCC (57 mg, 0.28 mmol) were sequentially added to carboxylic acid **8** (20 mg, 0.043 mmol) and alcohol **9** (31 mg, 0.086 mmol) in $CH_2Cl_2$ (5 mL) and this mixture stirred for 4 h. Rotary evaporation and chromatography (hexanes/$Et_2O$ 4:1) gave *t*-butyl ester **7** (17.2 mg, 0.021 mmol, 50%) as a colorless oil: $R_f$ 0.20 ($Et_2O$/hexanes 1:4); $[\alpha]_D^{25}$ +2.1 (*c* 1, $CHCl_3$); IR (KBr) 3487, 1730, 1369, 1225, 1153, 844 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.82−5.75 (m, 1H), 5.47−5.30 (m, 3H), 5.18 (d, $J$ = 3.2 Hz, 1H), 4.99 (q, $J$ = 7.1 Hz, 1H), 4.05 (d, $J$ = 0.9 Hz, 1H), 3.72 (d, $J$ = 17.4 Hz, 1H), 3.31 (ddd, $J$ = 10.1, 4.7, 3.4 Hz, 1H), 3.05 (d, $J$ = 17.4 Hz, 1H), 2.83 (dd, $J$ = 9.8, 5.3 Hz, 1H), 2.62 (dd, $J$ = 16.9, 10.0 Hz, 1H), 2.42 (dd, $J$ = 16.8, 4.7 Hz, 1H), 2.34 (ddd, $J$ = 12.9, 7.4, 5.3 Hz, 1H), 2.12−2.09 (*br*m, 4H), 2.03−1.91 (m, 3H), 1.48−1.44 (m, 36H), 1.27 (*br*s, 12H), 0.88 (t, $J$ = 6.9 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 174.9, 171.9, 170.4, 169.6, 168.9, 166.4, 135.0, 130.9, 128.2, 128.0, 83.8, 83.0, 81.9, 80.9, 79.7, 77.2, 75.2, 72.2, 46.4, 43.5, 40.4, 33.0, 32.1, 31.8, 30.5, 29.6, 29.4, 29.3, 28.0, 27.6, 27.2, 26.4, 22.6, 14.1; HRMS (ESI) calcd for $C_{44}H_{72}O_{13}Na$: $(M + Na)^+$, 831.4871, found: $(M + Na)^+$, 831.4853.

**Citrafungin A (1).** Pentaester **7** (15 mg, 6.3 $\mu$mol) in $CH_2Cl_2$ (5 mL) was treated at 20 °C with trifluoroacetic acid (2 mL). After 4 h, PhMe (10 mL) was added and solvent rotary evaporated to give crude citrafungin A (**1**) (11 mg, 6.3 $\mu$mol, 100%). Purification using reverse phase HPLC (column: Xbridge Prep C18 OBD 30 cm × 10 cm 5 $\mu$m (P/N186002982) and gradient elution $H_2O$/MeCN with 0.1% TFA 85:15 to 5.3:94.7 over 12 min) gave citrafungin A (**1**): $[\alpha]_D^{25}$ + 3.2 (*c* 0.25, MeOH); IR (KBr) 3453, 1731, 1405, 1250, 1187, 967 $cm^{-1}$; $^1H$ NMR (600 MHz, $d^6$-$Me_2CO$) $\delta$ 5.82 (dt, $J$ = 14.9, 6.3 Hz, 1H), 5.58 (dd, $J$ = 15.4, 7.4 Hz, 1H), 5.49 (d, $J$ = 3.4 Hz, 1H), 4.99 (q, $J$ = 7.1 Hz, 1H), 5.41−5.33 (m, 2H), 3.70 (d, $J$ = 16.3 Hz, 1H), 3.56 (ddd, $J$ = 8.8, 4.8, 3.7 Hz, 1H), 3.16 (d, $J$ = 16.3 Hz, 1H), 3.05 (dd, $J$ = 9.7, 5.8 Hz, 1H), 2.81 (dd, $J$ = 17.2, 9.4 Hz, 1H), 2.61 (dd, $J$ = 17.2, 4.9 Hz, 1H), 2.39 (ddd, $J$ = 13.2, 7.4, 6.0 Hz, 1H), 2.16−2.03 (m, 7H), 1.29 (*br*m, 12H), 0.87 (t, $J$ = 6.9 Hz, 3H); $^{13}C$ NMR (75 MHz, $d^6$-$Me_2CO$) $\delta$ 175.0, 173.8, 172.3, 171.1, 169.2, 169.0, 134.4, 130.6, 129.2, 128.8, 79.5, 75.6, 71.9, 46.2, 42.7, 40.8, 32.3, 32.0, 31.8, 30.9, 30.3, 27.2, 26.7, 22.7, 13.8; HRMS (ESI) calcd for $C_{28}H_{40}NaO_{13}$: $(M + Na)^+$, 607.2367, found: $(M + Na)^+$, 607.2363, calcd for $C_{28}H_{41}O_{13}$: $(M + H)^+$, 585.2547, found: $(M + H)^+$, 585.2550.

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**Supporting Information Available:** Experimental procedures, spectroscopic data, and copies of $^1H$ and $^{13}C$ NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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