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Ester Dienolate [2,3]-Wittig Rearrangement in Natural Product Synthesis: Diastereoselective Total Synthesis of the Triester of Viridiofungin A, A_2, and A_4

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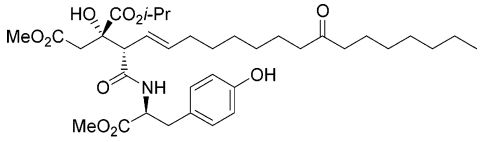
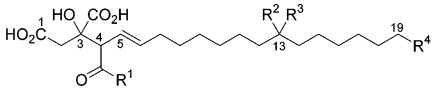


(3*S*,4*S*,5*E*,2′*S*)-viridiofungin A triester

An ester dienolate [2,3]-Wittig rearrangement was utilized to access the alkylated citric acid skeleton **6** that is characteristic for the viridiofungins and other members of the alkyl citrate family of secondary natural products. The [2,3]-sigmatropic rearrangement of (*Z*,*Z*)-**15** provided the rearrangement product (±)-*syn*-**16** in moderate yield and with very good diastereoselectivity. A Julia–Kocienski olefination efficiently served to connect the polar head (±)-*syn*-**26** with the lipophilic tail (**32a**–**c**) of the viridiofungins. Amide formation between the racemic viridiofungin precursors **35a**–**c** and the enantiomerically pure amino acid L-tyrosine methyl ester followed by preparative reversed-phase HPLC provided the isopropyl dimethyl ester of viridiofungin A ((+)-**39a**), A_2 ((+)-**39b**), and A_4 ((+)-**39c**) as well as the nonnatural diastereomers (−)-**38a**–**c**.

Introduction

The viridiofungins **1a**–**i** are secondary metabolites that have been isolated from the widely distributed filamentous soil fungi *Trichoderma viride* by solid fermentation (Figure 1).[1] The two-dimensional structure of VF_{A-C} (**1a**–**c**) as well as the trimethyl ester derivative of VF_A (Me_3-**1a**) was originally assigned on the basis of NMR studies and mass spectrometry.[2] The viridiofungins **1d**–**i** were isolated as minor compounds from the solid fermentation of *T. viride*.[3] The relative and absolute configuration of VF_A (**1a**) was assigned by comparison of the spectroscopic data of semi-synthetic and synthetic Me_3-**1a**. The first synthesis of Me_3-**1a** was accomplished by Hatakeyama in 1998.[4] The reported synthesis required a linear sequence of 27 steps and utilized a Katsuki-Sharpless asymmetric epoxidation[5] (87% *ee*) to set the absolute configuration of the crucial stereogenic quaternary carbon atom C3. In 2005, Hatakeyama reported a modified synthesis of the tri-*tert*-butyl ester (t-Bu)$_3$-**1a** and, following acidic hydrolysis of the *tert*-butyl ester functionalities, of (−)-viridiofungin A (**1a**).[6] Hatakeyama's second generation synthesis of VF_A (**1a**) required 22 steps and



compd	VF	R^1	R^2	R^3	R^4
1a	A	tyr	=O		Me
1b	B	phe	=O		Me
1c	C	trp	=O		Me
1d	A_1	tyr	OH	H	Me
1e	A_2	tyr	H	H	Me
1f	B_2	phe	H	H	Me
1g	Z_2	OH	H	H	Me
1h	A_3	tyr	=O		H
1i	A_4	tyr	=O		*n*-Pr

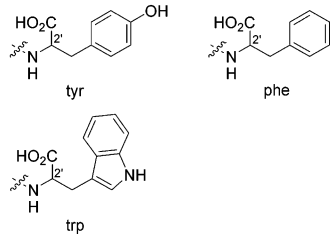


FIGURE 1. Reported structures of the viridiofungins **1a**–**i**.

† Undergraduate research participants.

‡ Deceased on September 28, 2003.

(1) Mandala, S. M.; Harris, G. H. *Methods Enzymol.* **1999**, *311*, 335–348.

(2) Harris, G. H.; Turner Jones, E. T.; Meinz, M. S.; Nallin-Omstead, M.; Helms, G. L.; Bills, G. F.; Zink, D.; Wilson, K. E. *Tetrahedron Lett.* **1993**, *34*, 5235–5238.

(3) Mandala, S. M.; Thornton, R. A.; Frommer, B. R.; Dreikorn, S.; Kurtz, M. B. *J. Antibiot.* **1997**, *50*, 339–343.

(4) Esumi, T.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Tetrahedron Lett.* **1998**, *39*, 877–880.

(5) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.

(6) Morokuma, K.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Chem. Commun.* **2005**, 2265–2267.

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elegantly utilized a cross-metathesis strategy to construct the isolated C5/C6 double bond with an *E*/*Z*-ratio of 88/12.

The viridiofungins are potent broad spectrum fungicidal compounds and were originally isolated as part of a natural product screening program toward inhibitors of the squalene synthase.[7] The viridiofungins A−C (**1a**−**c**) inhibit in vitro the squalene synthase of *Saccharomyces cerevisiae* and *Candida albicans* in micromolar concentrations. However, they are 1000-fold less active then zaragozic acid A (**5**).[8] Furthermore, it was demonstrated that the antifungal activity of the viridiofungins in vivo is not a consequence of the squalene synthase inhibition. Further analysis of the molecular mode of action of the viridiofungins revealed that they are nanomolar inhibitors of the serine palmitoyltranferase (SPT) of *C. albicans* and HeLa cells in vitro.[3] Interestingly, the SPT of *S. cerevisiae* is much less sensitive to the viridiofungins and the antifungal activity in this case is apparently a consequence of multiple mechanisms of action. The SPT is a pyridoxal 5′-phosphate-dependent enzyme that condenses serine with palmitoyl-CoA as first step of the sphingolipid biosynthesis in mammalian and fungal cells.[9] Besides their ability to interfere with the sphingolipide and the squalene biosynthesis, the viridiofungins are also inhibitors of the farnesyl transferase and the farnesylation of the oncogenic Ras protein and thus potentially useful in treating cancer.[10,11]

Structurally, the viridiofungins (**1**) are members of the alkyl citrate family of natural products. Other representatives of this class of secondary metabolites are trachyspic acid (**2**),[12,13] citrafungin A (**3**),[14] L-731,120 (**4**),[15] and zaragozic acid A (**5**)[16,17,18] (Figure 2). Natural products **1**−**5** contain a citric acid structural element **6** (Figure 3) that is alkylated in the 2-position with a lipophilic tail

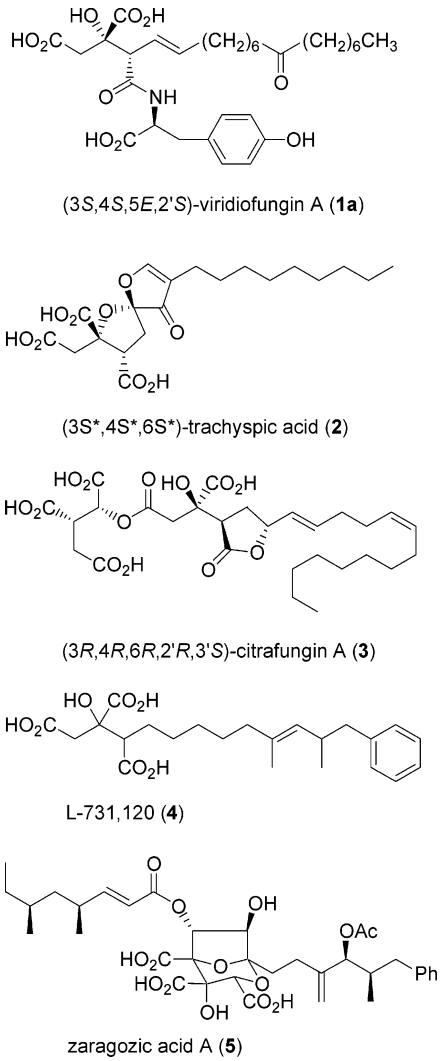

FIGURE 2. Natural products containing the alkyl citrate structural element.

featuring a varying number of carbon atoms and different further functional groups. In the case of zaragozic acid A (**5**), the hydroxylation of carbon atoms C2 and C4 leads to the formation of the characteristic bicyclic ring system by an intramolecular ketalization. The viridiofungins (**1**) are distinguished from the other alkylated citric acid natural products **2**−**5** by the presence of an aromatic amino acid.

For the past several years, we have been investigating the ester *di*enolate [2,3]-Wittig rearrangement as a tool for the diastereoselective construction of 3-alkoxycarbonyl-3-hydroxy-substituted 1,5-hexadienes.[19] To demonstrate the usefulness of this novel variation of the classical [2,3]-Wittig rearrangement in target-oriented

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(8) Onishi, J. C.; Milligan, J. A.; Basilio, A.; Bergstrom, J.; Curotto, J.; Huang, L.; Meinz, M.; Nallin-Omstead, M.; Pelaez, F.; Rew, D.; Salvatore, M.; Thompson, J.; Vicente, F.; Kurtz, M. B. *J. Antibiot.* **1997**, *50*, 335−338.

(9) For reviews concerning the bisynthesis and the biological functions of sphingolipids, see: (a) Kolter, T.; Sandhoff, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1532−1568. (b) Chen, J. K.; Lane, W. S.; Schreiber, S. L. *Chem. Biol.* **1999**, *6*, 221−235. (c) Linn, S. C.; Kim, H. S.; Keane, E. M.; Andras, L. M.; Wang, E.; Merrill, A. H. *Biochem. Soc. Trans.* **2001**, *29*, 831−835. (d) Merrill, A. H. *J. Biol. Chem.* **2002**, *277*, 25843−25846. Radin, N. S. *Biochem. J.* **2003**, *371*, 243−256.

(10) Meinz, M. S.; Pelaez, F.; Omstead, M. N.; Milligan, J. A.; Diez, M. T.; Onishi, J. C.; Bergstrom, J. A.; Jenkins, R. F.; Harris, G. H.; Jones, E. T. T.; Huang, L.; Kong, Y. L.; Lingham, R. B.; Zink, D. Eur. Pat. Appl. EP 526,936 (Cl. C07C235/76), 1993; *Chem. Abstr.* **1993**, *118*, 183428t.

(11) For reviews concerned with the potential of farnesyltransferase inhibitors in cancer chemotherapy, see: (a) Wittinghofer, A.; Waldmann, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 4192−4214. (b) Bell, I. M. *J. Med. Chem.* **2004**, *47*, 1869−1878.

(12) Isolation, see: Shiozawa, H.; Takahashi, M.; Takatsu, T.; Kinoshita, T.; Tanzawa, K.; Hosoya, T.; Furuya, K.; Takahashi, S.; Furihata, K.; Seto, H. *J. Antibiotics* **1995**, *48*, 357−362.

(13) Total synthesis, see: Hirai, K.; Ooi, H.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 857−859.

(14) Singh, S. B.; Zink, D. L.; Doss, G. A.; Polishook, J. D.; Ruby, C.; Register, E.; Kelly, T. M.; Bonfiglio, C.; Williamson, J. M.; Kelly, R. *Org. Lett.* **2004**, *6*, 337−340.

(15) Harris, G. H.; Dufresne, C.; Joshua, H.; Koch, L. A.; Zink, D. L.; Salmon, P. M.; Goklen, K. E.; Kurtz, M. M.; Rew, D. J.; Bergstrom, J. D.; Wilson, K. E. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2403−2408.

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(17) For a recent review on the total synthesis of zaragozic acids, see: Jotterand, N.; Vogel, P. *Curr. Org. Chem.* **2001**, *5*, 637−661.

(18) The biosynthesis of zaragozic acid A has been investigated; see: Byrne, K. M.; Arison, B. H.; Nallin-Omstead, M.; Kaplan, L. *J. Org. Chem.* **1993**, *58*, 1019−1024. Although details of the biosynthesis of the viridiofungins have not been reported, analogies may be reasonable.

(19) (a) Hiersemann, M.; Abraham, L.; Pollex, A. *Synlett* **2003**, 1088−1095. (b) Hiersemann, M. *Eur. J. Org. Chem.* **2001**, 483−491. (c) Hiersemann, M. *Synlett* **2000**, 415−417. (d) Hiersemann, M.; Lauterbach, C.; Pollex, A. *Eur. J. Org. Chem.* **1999**, 2713−2724. (e) Hiersemann, M. *Tetrahedron* **1999**, *55*, 2625−2638.

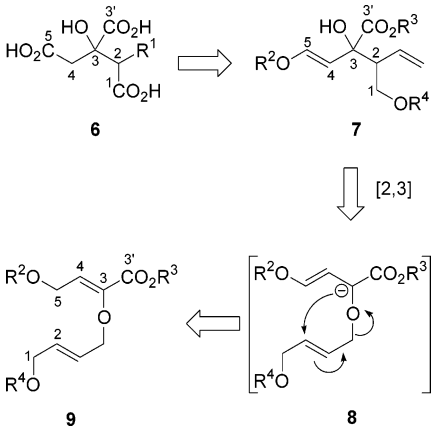
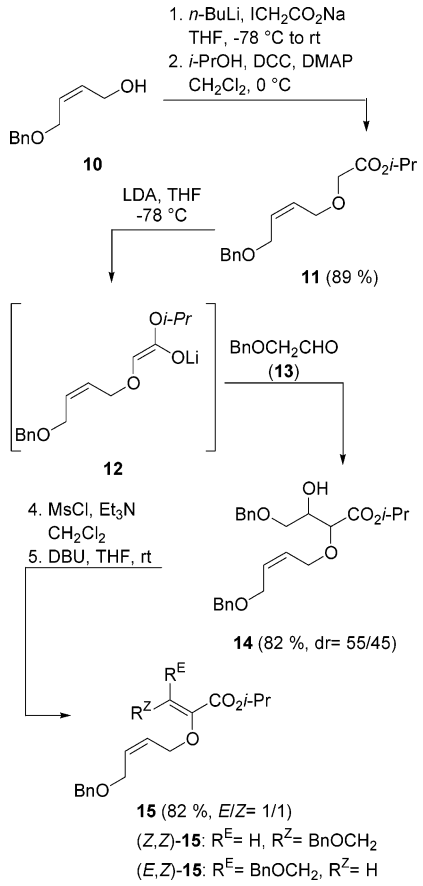


FIGURE 3. Proposed synthetic access to alkylated citric acids (**6**).

synthesis,[20−22] we designed a synthetic plan toward the viridiofungins which may be generalized to provide access to other members of the alkyl citrate family. As depicted in Figure 3, we envisioned that the generation of the ester dienolate **8** by treatment of the α-allyloxy-substituted α,*β*-unsaturated ester **9** with a suitable base would be followed by a [2,3]-Wittig rearrangement to afford the highly substituted 1,5-hexadiene **7**. The rearrangement product **7** already contains the major structural elements required for synthetic access to alkylated citric acids (**6**). The tertiary alcohol at C3 along with the vicinal stereogenic carbon atom C2 are generated by the CC-connecting sigmatropic event. The relative configuration of the two stereogenic centers (C3, C2) would be a consequence of the simple diastereoselectivity of the [2,3]-Wittig rearrangement. The crucial carboxylic acid functions are introduced as an ester (C3′), an enol ether (C5), and a protected alcohol (C1) and, therefore, are easily to manipulate individually. Finally, our plan was to utilize the vinyl substituent at the C2 as a versatile connecting point for the introduction of the lipophilic segment (R^1) that is characteristic for natural products of the alkyl citrate family. In the context of the viridiofungin synthesis, we intended to exploit this highly convergent approach for the synthesis of viridiofungin A (for comparison of authentic synthetic and semisynthetic material), A_2 (lacking the C13-keto carbonyl group), and A_4 (containing a C_{22}-carbon chain) which have not been synthesized previously.[23] Viridiofungin A_4 is a minor compound from the viridiofungin fermentation but is the most potent compound in inhibiting the *C. albicans* SPT (IC_{50} 3.2 ng/mL).[3]

To demonstrate the feasibilty of our approach toward alkylated citric acid derivatives, we report complete

SCHEME 1. Synthesis of 15



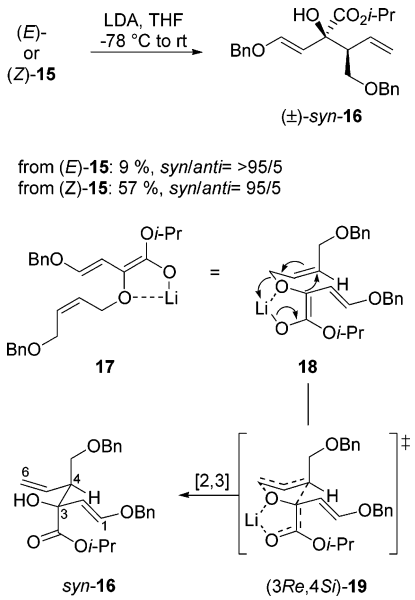
details of the synthesis of triesters of viridiofungin A, A_2, and A_4 as well as three nonnatural diastereomers thereof.[24]

Results and Discussion

The envisaged dienolate [2,3]-Wittig rearrangement required convenient multigram access to the α-alloxy-substituted α,*β*-unsaturated ester **15** (Scheme 1). Therefore, we developed a five-step sequence to **15** that was routinely performed on a 10 g scale. The synthesis embarked with the etherification of the mono-benzylated (*Z*)-2-butene-1,4-diol (**10**) with the commercially available sodium salt of iodoacetic acid followed by esterification with 2-propanol in the presence of DCC and catalytic amounts of DMAP[25] to provide the allyloxy acetate **11**. An aldol condensation process was recruited to construct the vinyl ether double bond of **15**. The three-step procedure consisted of an aldol addition of **11** with benzyloxy acetaldehyde **13** followed by mesylation of the *β*-hydroxy ester **14** and DBU-mediated elimination of the corresponding mesylate. It was pivotal for the success of the aldol reaction to maintain the reaction temperature below −70 °C in order to prevent the competing ester enolate [2,3]-Wittig rearrangement of the intermediate allyloxy-substitued enolate **12**.[22] The aldol condensation afforded the allyl vinyl ether **15** as a 1/1 mixture of vinyl ether double bond isomers. The double-bond diastereomers

(20) Wittig, G.; Döser, H.; Lorenz, I. *Justus Liebigs Ann. Chem.* **1949**, *562*, 192−205.
(21) First examples of an ester enolate [2,3]-Wittig rearrangement, see: (a) Takahashi, O.; Saka, T.; Mikami, K.; Nakai, T. *Chem. Lett.* **1986**, *9*, 1599−1602. (b) Raucher, S.; Gustavson, L. M. *Tetrahedron Lett.* **1986**, *27*, 1557−1560. (c) Uchikawa, M.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 4581−4582.
(22) For reviews, see: (a) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885−902. (b) Mikami, K.; Nakai, T. *Synthesis* **1991**, 594−604.
(23) The configuration of viridiofungin A_2 and A_4 was assigned in analogy to the known configuration of viridiofungin A.
(24) For a preliminary communication, see: Pollex, A.; Abraham, L.; Müller, J.; Hiersemann, M. *Tetrahedron Lett.* **2004**, *45*, 6915−6918.
(25) Neises, B.; Steglich, W. *Angew. Chem.* **1978**, *90*, 556−557.

SCHEME 2. Ester Dienolate [2,3]-Wittig Rearrangement



(*E*,*Z*)- and (*Z*,*Z*)-**15** can be separated by preparative HPLC or carefully performed flash chromatography.[26]

With the double bond isomerically pure allyl vinyl ether (*E*)- and (*Z*)-**15** in hand, the crucial ester dienolate [2,3]-Wittig rearrangement was next investigated (Scheme 2). In the event, a variety of different bases, solvents, and temperature protocols were utilized. However, none of the employed conditions improved the chemoselectivity of the rearrangement compared to the simplest procedure (slight excess of LDA, THF, −78 to −10 °C). Furthermore and somewhat surprisingly, the chemoselectivity depended considerably on the vinyl ether double-bond configuration. Whereas (*E*,*Z*)-**15** underwent the rearrangement in low yield with varying amounts of reisolated starting material and a multitude of unidentified decomposition products, (*Z*,*Z*)-**15** afforded the product (±)-s*yn*-**16** of the ester dienolate [2,3]-Wittig rearrangement in acceptable yield and excellent simple diastereoselectivity in favor of the desired *syn*-configured diastereomer. The exact reason(s) of the discrepancy remains speculative, but we assume the deprotonation rather than the rearrangement as the decisive step. The consistency of yield and diastereoselectivity for the rearrangement of (*Z*,*Z*)-**15** in the absence of additional Lewis bases or metal salts even on a 5 g scale accounts for the usefulness of the rearrangement. Although the rearrangement can be performed with the mixture of double bond diastereomers (*E*,Z)- and (*Z*,*Z*)-**15**, we generally preferred to utilize the double bond isomerically pure (*Z*,*Z*)-**15** as substrate for the rearrangement.

The qualitative analysis of the stereochemical course of the rearrangement rests on the formation of the chelated lithium ester dienolate **17** (Scheme 2). The rearrangement would then proceed through the bicyclo-[3.3.0]octane-type transition state (3*Re*,4*Si*)-**19** in which the bulky benzyloxymethyl group at C4 preferentially adopts a position directed toward the convex face of the bicyclic transition state (3*Re*,4*Si*)-**19**. Thus, the relative

(26) For details, see the Experimental Section.

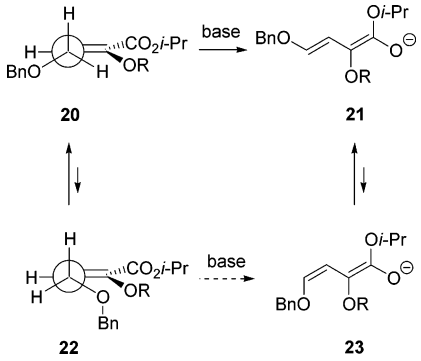


FIGURE 4. Diastereoselective generation of the ester dienolate **21**.

configuration of the rearrangement product is defined by the configuration of the allylic ether double bond. The discussed stereochemical course of the rearrangement is in accordance with previous mechanistic work concerned with the ester dienolate [2,3]-Wittig rearrangement. These studies revealed a general relationship between the allylic ether double bond configuration and the relative configuration of the rearrangement product ("*E* to *anti*" and "*Z* to *syn*").[19]

Although not of primary importance for the course of the viridiofungin synthesis, it is worth mentioning that the rearrangement product **16** was isolated exclusively with an *E*-configured enol ether double bond. The *E*-configuration was assigned based on NOE spectroscopy. As depicted in Figure 4, the 1,3-allylic strain[27] between the benzyloxy and the allyloxy (OR) substituent in **22** destabilizes the corresponding transition state that would lead to the (*Z*,*E*)-configured ester dienolate **23**. Alternatively, the preferred formation of the (*E*,*E*)-configured dienolate **21** could also be the consequence of thermodynamic isomerization process between the dienolates **21** and **23**.

After having successfully realized the key C−C-connecting transformation, it was required to convert the enol ether into a carboxyl group at C1. As depicted in Scheme 3, acidic hydrolysis of the benzyl vinyl ether afforded an aldehyde that was immediately oxidized to the corresponding acid which was then esterificated[25] to afford the methyl ester (±)-*syn*-**24**. It was anticipated to complete the carbon skeleton of the viridiofungins by coupling of a C5 aldehyde with the lipophilic C6−C20(C22) segments. In compliance with this plan, the tertiary alcohol was protected[28] as a silyl ether[29] and the oxidative cleavage of the terminal double bond by ozonolysis provided the desired instable C-5 aldehyde (±)-*syn*-**26** that was immediately used for the succeeding attachment of the lipophilic segment.

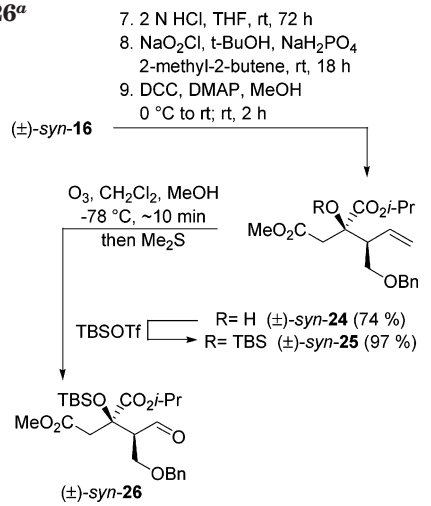
The isolated *E*-configured C5-C6 double bond that joins together the polar head with the lipophilic tail of the viridiofungins was the second key C−C-connecting trans-

(27) (a) Johnson, F.; Malhotra, S. K. *J. Am. Chem. Soc.* **1965**, *87*, 5492−5493. (b) Malhotra, S. K.; Johnson, F. *J. Am. Chem. Soc.* **1965**, *87*, 5493−5495. (c) Johnson, F. *Chem. Rev.* **1968**, *68*, 375−413. (d) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

(28) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455−3458.

(29) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031−1069.

SCHEME 3. Preparation of the Aldehyde (±)-*syn*-26[a]

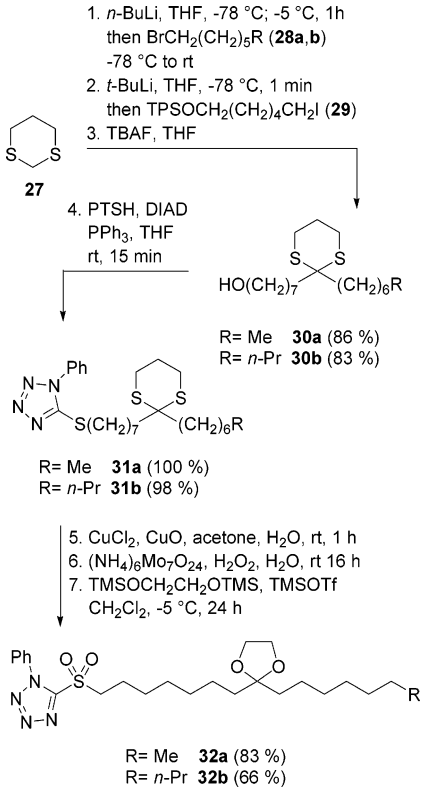


[a] Key: TBS = *tert*-butyldimethylsilyl.

formation we faced. Kocienski's modification[30] of the Julia olefination[31] is being applied frequently[32] to construct isolated *E*-configured double bonds. Therefore, we decided to follow this proven path and to attempt a construction of the C5−C6 double bond by a Julia−Kocienski olefination.[33]

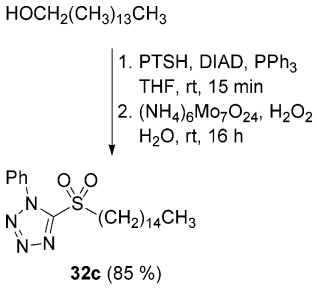
The sulfones **32a**,**b** required for the envisioned olefination were synthesized by a strategy that relied on a sequential 1,3-dithiane alkylation (Scheme 4).[34] The initial alkylation of the lithiated 1,3-dithiane **27** with either 1-bromoheptane **28a** or 1-bromononane **28b** was realized according to the original Corey−Seebach procedure.[35] The second alkylation with the alkyl iodide **29** required the modified conditions (*t*-BuLi, HMPA) originally described by Williams.[36] Cleavage of the *tert*-butyldiphenylsilyl (TPS) protecting group afforded the alcohols **30a**,**b** that were converted into the 5-alkylsulfanyl-1-phenyl-1*H*-tetrazole derivatives **31a**,**b** by a high-yielding Mitsunobu procedure.[30,37] Our initial attempts to chemoselectively oxidize the sulfide to the sulfone in the presence of the thioketal were unsuccessful. Therefore, the thioketal was cleaved by treatment with Cu^{II}

SCHEME 4. Preparation of the Sulfones 32a,b Required for the Julia−Kocienski Olefination[a]



[a] Key: TPS = *tert*-butyldiphenylsilyl, PTSH = 1-phenyl-1*H*-tetrazole-5-thiol, DIAD = diisopropyl azodicarboxylate.

SCHEME 5. Preparation of the Sulfone 32c



in water[38] followed by the oxidation of the sulfide to the sulfone. Not surprisingly, all attempts to perform the following Julia−Kocienski olefination in the presence of the unprotected ketone failed to provide the desired coupling product. Therefore, the keto carbonyl group of the sulfone was converted into the cyclic ketales **32a**,**b** utilizing Noyori's conditions.[39] Accordingly, the sulfone **32c** required for the synthesis of viridiofungin A_2 was prepared from the commercially available 1-pentadecanol in two steps (Scheme 5).

Our original proposal that a Julia−Kocienski olefination may be suitable in order to connect the polar head with the lipophilic tail of the viridiofungins proved to be correct (Scheme 6). Treatment of either one of the sulfones **33a**−**c** with potassium hexamethyldisilazide

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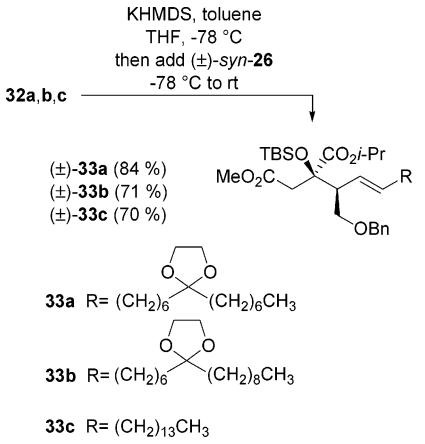
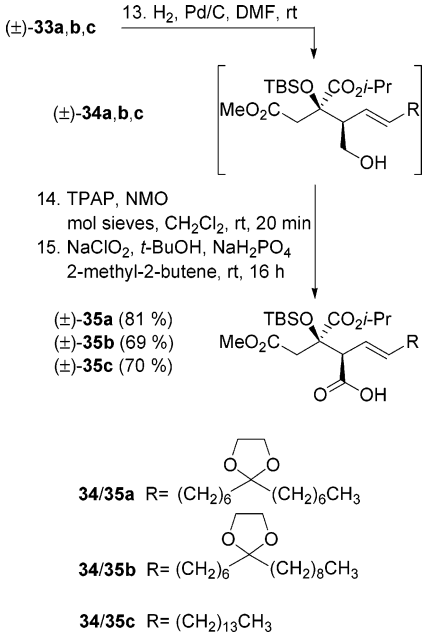
SCHEME 6. Julia-Kociensky Olefination[a]



[a] Key: KHMDS = $K[N(SiMe_3)_2]$.

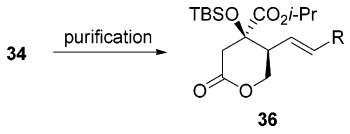
SCHEME 7. Generation of the 4′-Carboxyl Function



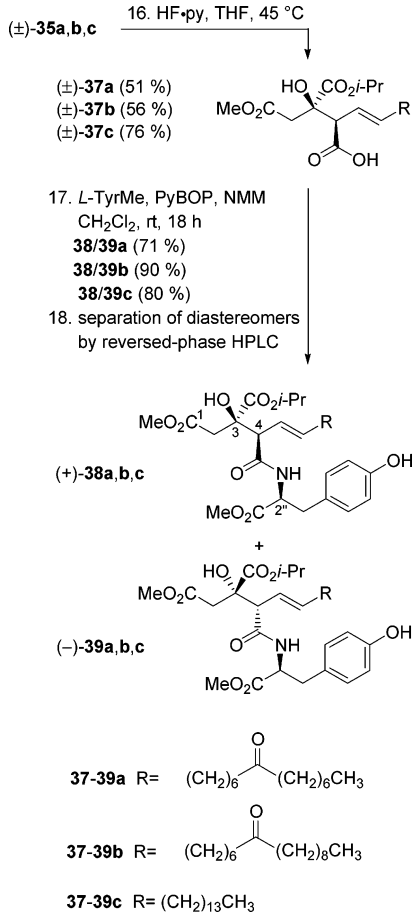
(KHMDS) at low temperature followed by the addition of the aldehyde (±)-*syn*-**26** provided the coupling products **33a**−**c** in good yield and as a single *E*-configured double-bond isomer.[40]

Having completely assembled the carbon skeleton of the viridiofungins, the 4′-benzyloxymethyl group had to be converted into a carboxyl function in preparation of the amide formation with L-tyrosine methyl ester (Scheme 7). For this purpose, the benzyl protecting group was chemoselectively removed in the presence of the isolated double bond by hydrogenolysis. The primary alcohols (±)-**34a**−**c** were immediately oxidized with tetra-*n*-propylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) without purification.[41] Oxidation of the aldehydes afforded the stable acids (±)-**35a**−**c**. Attempts to purify the alcohols **34a**−**c** by flash chromatography inevitable led to the formation of the corresponding lactone **36** (Scheme 8).

SCHEME 8. Undesired Lactonization



SCHEME 9. Final Steps of the Synthesis of Triesters of Natural 39a−c and Nonnatural Viridiofungin Diastereoisomers 38a−c



The concluding steps of the synthesis are depicted in Scheme 9. The remaining TBS and ketale protecting group of **35a**,**b** were removed in a single step with HF in pyridine to afford the acids **37a**,**b**. The removal of the silyl protecting group of the acid **35c** provided the acid **37c** which represents the diester derivative of (±)-viridiofungin Z_2 (**1h**). The appropriate reagent combination for amide bond formation between the acids **37a**−**c** and L-tyrosine methyl ester (L-TyrMe) was identified after some experimentation.[42] Benzotriazolyloxytris(pyr-

(40) To validate the exclusive formation of the (*E*)-configured double bond, the corresponding (*Z*)-configured double bond isomer was synthesized by a Wittig olefination. NOE spectroscopy and comparison of the coupling constants of the vinylic protons support the assignment of the double bond configuration and demonstrate the very high and dependable preference of the Julia−Kocienski olefination for the formation of the (*E*)-configured olefin (±)-*syn*-**33a**. See the Supporting Information for details. Utilizing LiHMDS instead of KHMDS for the Julia−Kocienski olefination led to inferior *E*/*Z* selectivities.

(41) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.

(42) For a recent review on peptide coupling reagents in organic synthesis, see: Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447−2467.

rolidino)phosphonium hexafluorophosphate (PyBOP)[43] in combination with *N*-methylmorpholine (NMM) mediated the coupling of the racemic acids **37a**−**c** with the enantiomerically pure L-TyrMe to afford diastereomeric mixtures of the natural (**39a**−**c**) and nonnatural (**38a**−**c**) viridiofungin A, A_2, and A_4 triester derivatives. Preparative reversed-phase HPLC was employed to separate the mixture of diastereoisomers. Thus, the triester derivatives of the natural (−)-viridiofungin A (**39a**), (−)-A_4 (**39b**), and (−)-A_2 (**39c**) as well as the nonnatural diastereoisomers thereof ((+)-**38a**−**c**) were isolated as single diastereoisomers. Comparison of the spectroscopic data of the isopropyl dimethyl ester **39a** with data reported[44] for the synthetic viridiofungin A trimethyl (−)-Me_3-**1a** and tri-*tert*-butyl ester[6] (−)-(*tert*-Bu)$_3$-**1a** support the structural assignment of **39a** as the diastereoisomer with the natural configuration.

In summary, we have established a short, reliable, and flexible approach toward four natural and three nonnatural viridiofungins. The ester dienolate [2,3]-Wittig rearrangement effectively served to construct the polar head of the viridiofungins A, A_4, A_2, and Z. Our highly convergent approach is suitable for the diversified synthesis of further viridiofungins which provides opportunity to study the pharmacological properties of a wide variety of natural and nonnatural viridiofungins.

Experimental Section[45]

Ester 11. To a stirred solution of (*Z*)-4-benzyloxybut-2-en-1-ol **10** (11.11 g, 62.2 mmol, 1.0 equiv) in THF (1 mL/mmol) was added *n*-BuLi (2.4 M in hexane, 25.9 mL, 62.2 mmol, 1.0 equiv) at −78 °C followed by the addition of solid iodoacetic acid sodium salt (13.57 g, 65.3 mmol, 1.05 equiv). The cooling bath was removed, and the suspension was allowed to stir overnight. The reaction was then quenched by the addition of aq 1 N KOH (90 mL). The phases were separated, and the organic phase was extracted twice with aq 1 N KOH (30 mL). The aqueous phase was acidified by the addition of concd HCl (pH < 4) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification by Kugelrohr distillation (150 °C, 0.1 mbar) afforded (*Z*)-(4-benzyloxybut-2-enyloxy)acetic acid (14.02 g, 59.3 mmol, 95%) as a brown oil.

To an ice-cooled solution of the acid (7.10 g, 30.1 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL/mmol of the acid) at 0 °C were added DMAP (0.18 g, 1.5 mmol, 0.05 equiv), DCC (6.83 g, 33.1 mmol, 1.1 equiv), and the 2-propanol (4.6 mL, 60.2 mmol, 2.0 equiv). The resulting mixture was stirred for 30 min at ambient temperature. The precipitate was then removed by filtration and washed with CH_2Cl_2, and the solvent was evaporated under reduced pressure. Flash chromatography (heptane/ethyl acetate 5/1) afforded the ester **11** (7.9 g, 28.4 mmol, 94%) as a yellow oil: R_f 0.65 heptane/ethyl acetate 1/1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.23 (m, 5H), 5.88−5.70 (m, 2H), 5.10 (sept, J = 6.3 Hz, 1H), 4.50 (s, 2H), 4.15 (d, J = 5.7 Hz, 2H), 4.09 (d, J = 5.6 Hz, 2H), 4.01 (s, 2H), 1.25 (d, J = 6.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 (C), 138.1 (C), 130.3 (CH), 128.6 (CH), 128.4 (2 × CH), 127.8 (2 × CH), 127.7 (CH), 72.3 (CH_2), 68.5 (CH_2), 67.5 (CH_2), 66.9 (CH), 65.7 (CH_2), 21.8 (2 × CH_3); IR (in substance) ν 2980−2860, 1750 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.06; H, 8.19.

β-Hydroxy Ester 14. To a stirred solution of LDA [prepared in situ from diisopropylamine (7.8 mL, 55.4 mmol, 1.3 equiv) and *n*-BuLi (2.31 M in hexane, 22.2 mL, 51.2 mmol, 1.2 equiv)] in THF (1 mL/mmol **11**) was added a cooled solution (−78 °C) of the ester **11** (11.86 g, 42.6 mmol, 1.0 equiv) in THF (1 mL/mmol **11**) at −78 °C. The solution was stirred for 15 min, and the freshly prepared aldehyde **13** (8.31 g, 55.4 mmol, 1.2 equiv) was added as cooled solution (−78 °C) in THF (0.5 mL/mmol **13**). The mixture was stirred for 30 min at −78 °C and then quenched by the addition of saturated aq NH_4Cl at −78 °C. After dilution with H_2O and CH_2Cl_2, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Flash chromatography (heptane/ethyl acetate 3/1 to 1/1) afforded the β-hydroxy ester **14** [15.0 g, 34.9 mmol, 82%, mixture of diastereomers (dr 55:45)] as pale yellow oil:. R_f 0.35 heptane/ethyl acetate 1/1; ^{1}H NMR (500 MHz, $CDCl_3$) mixture of diastereomers δ 7.38−7.27 (m, 10H), 5.84−5.75 (m, 1H), 5.73−5.67 (m, 1H), 5.08 (br sept, J = 6.3 Hz, 1H), 4.52 (dd, J = 8.2, 4.4 Hz, 2H), 4.48 (d, J = 1.6 Hz, 2H), 4.28 (dd, J = 12.5, 5.8 Hz, 1 H^{minor}), 4.21 (dd, J = 12.1, 6.2 Hz, 1 H^{major}), 4.11−3.93 (m, 4H), 4.00 (d, J = 3.6 Hz, 1H^{minor}) 3.96 (d, J = 5.8 Hz, 1H^{major}), 3.64−3.53 (m, 2H), 2.58 (d, J = 6.5 Hz, 1H^{major}), 2.46 (d, J = 7.5 Hz, 1H^{minor}), 1.28−1.16 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) mixture of diastereomers δ 170.3 (C-minor), 170.2 (C-major), 138.0 (C), 137.8 (C), 130.33 (CH-major), 130.28 (CH-minor), 128.5 (2 × CH), 128.4 (4 × CH), 127.80 (2 × CH), 127.76 (2 × CH), 127.7 (CH), 78.9 (CH-major), 77.8 (CH-minor), 73.45 (CH_2-major), 73.42 (CH_2-minor), 72.4 (CH_2), 71.2 (CH), 70.1 (CH_2-minor), 70.0 (CH_2-major), 68.92 (CH-minor), 68.88 (CH-major), 66.43 (CH_2-minor), 66.40 (CH_2-major), 65.7 (CH_2), 21.8 (CH_3), 21.7 (CH_3); IR (in substance) ν 3550−3420, 2980−2875, 1730 cm^{-1}. Anal. Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. found: C, 70.26; H, 7.83.

Allyl Vinyl Ether 15. To a solution of the diastereomeric β-hydroxy ester **14** (15.03 g, 35.1 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL/mmol **14**) at 0 °C were added Et_3N (6.3 mL, 45.6 mmol, 1.3 equiv) and MsCl (3.3 mL, 42.1 mmol, 1.2 equiv). The reaction mixture was stirred for 30 min at ambient temperature, quenched with saturated aq $NaHCO_3$, and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude mesylate **43** which was dissolved in THF (2 mL/mmol of the mesylate) and cooled to 0 °C. DBU (16 mL, 105 mmol, 3.0 equiv) was added at 0 °C. The reaction mixture was stirred at ambient temperature until TLC indicated complete consumption of the starting material (about 12 h). The reaction was then quenched with H_2O (70 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Flash chromatography (heptane/ethyl acetate 10/1) afforded the allyl vinyl ether **15** (11.8 g, 28.8 mmol, 82%) as mixture of double bond isomers (*E*,*Z*/*Z*,*Z* = 50:50): R_f 0.59 heptane/ethyl acetate 1/1. The double-bond isomers were separated by preparative HPLC, column: 32 × 250 mm, Nucleosil 50−5, 5 μm, solvent: (heptane/ethyl acetate 4/1, flow: 30 mL/min, t_R (*Z*,*Z*-**15**) ∼ 16 min, t_R (*E*,*Z*-**15**) ∼ 19 min**,** performance: ∼ 1 g/h).

(*E*,*Z*)-15: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.26 (m, 10H, C*H*-Ar), 5.81−5.79 (m, 2H, 4- and 5-C*H*═), 5.29 (t, J = 5.8 Hz, 1H, 2′-C*H*═), 5.10 (sept, J = 6.3 Hz, 1H, O*i*PrC*H*), 4.53 (s, 2H, 2″-CH_2Ph), 4.51 (s, 2H, 6-CH_2Ph), 4.48 (d, J = 5.8 Hz, 2H, 2″-CH_2OBn), 4.34 (br d, J = 3.7 Hz, 2H, 3-CH_2), 4.10 (br d, J = 4.3 Hz, 2H, 6-CH_2OBn), 1.26 (d, J = 6.3 Hz, 6H, O*i*PrCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7 (1-*C*), 145.4 (2-*C*═), 138.1 (*C*-Ar), 137.9 (*C*-Ar), 129.8 (5-*C*H═), 128.41 (2 × *C*H-Ar), 128.39 (2 × *C*H-Ar), 127.83 (2 × *C*H-Ar), 127.77 (2 × *C*H-Ar), 127.70 (*C*H-Ar), 127.67 (*C*H-Ar), 127.4 (4-*C*H═), 112.1 (2′-*C*H═), 72.5 (2″-CH_2Ph), 72.4 (6-*C*H_2Ph), 69.1 (O*i*Pr*C*H), 66.6 (2″-*C*H_2), 65.9 (6-*C*H_2), 64.7 (3-*C*H_2), 21.7 (2 × O*i*Pr*C*H_3);

(43) Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 205−208.

(44) We thank Prof. Susumi Hatakeyama for providing us with copies of NMR spectra of the synthetic viridiofungin A trimethylester Me_3-**1a**.

(45) For general experimental methods consult the Supporting Information.

IR (in substance) ν 3090−3030, 2980−2860, 1720 cm^{-1}. Anal. Calcd for $C_{25}H_{30}O_5$: C, 73.15; H, 7.37. Found: C, 73.31; H, 7.64.

(*Z,Z*)-15: ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.28 (m, 10H, C*H*-Ar), 6.35 (t, J = 6.3 Hz, 1H, 2′-C*H*=), 5.80−5.73 (m, 2H, 4- and 5-C*H*=), 5.07 (sept, J = 6.3 Hz, 1H, O*i*PrC*H*), 4.50 (s, 2H, 2″-CH_2Ph), 4.47 (s, 2H, 6-CH_2Ph), 4.44 (d, J = 6.2 Hz, 2H, 3-CH_2), 4.24 (d, J = 6.3 Hz, 2H, 2″-CH_2), 4.06 (d, J = 6.4 Hz, 2H, 6-CH_2), 1.27 (d, J = 6.3 Hz, 6H, O*i*PrCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6 (1-*C*), 145.7 (2-*C*=), 138.0 (*C*-Ar), 137.9 (*C*-Ar), 130.6 (5-*C*H=), 128.43 (2 × *C*H-Ar), 128.41 (2 × *C*H-Ar), 127.9 (*C*H-Ar), 127.83 (2 × *C*H-Ar), 127.78 (*C*H-Ar), 127.76 (2 × *C*H-Ar), 127.7 (4-*C*H=), 124.3 (2′-*C*H=), 72.8 (2″-*C*H_2Ph), 72.4 (6-*C*H_2Ph), 68.9 (O*i*Pr*C*H), 67.5 (3-*C*H_2), 65.6 (6-*C*H_2), 64.5 (2″-*C*H_2), 21.8 (2 × O*i*PrCH_3); IR (in substance) ν 3090−3030, 2980−2860, 1720 cm^{-1}. Anal. Calcd for $C_{25}H_{30}O_5$: C, 73.15; H, 7.37. Found: C, 73.03; H, 7.58.

α-Hydroxyester (±)-*syn*-16. To a stirred solution of LDA [prepared in situ from diisopropylamine (1.7 mL, 12.0 mmol, 1.2 equiv) and *n*-BuLi (2.3 M in hexane, 4.6 mL, 10.5 mmol, 1.05 equiv)] in THF (4 mL/mmol **15**) was added a cooled solution (−78 °C) of the allyl vinyl ether (*Z,Z*)-**15** (4.11 g, 10.0 mmol, 1.0 equiv) in THF (2 mL/mmol **15**) at −78 °C. The solution was allowed to warm to −10 °C overnight, quenched with saturated aq NH_4Cl, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Flash chromatography (heptane/ethyl acetate 20/1 to 10/1) afforded the rearrangement product **16** (2.36 g, 5.7 mmol, 57%, *syn*/*anti* = 95:5): R_f 0.59 heptane/ethyl acetate 1/1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.24 (m, 10H), 6.71 (d, J = 12.7 Hz, 1H, 2″-C*H*=), 5.84 (ddd, J = 16.8, 10.5, 9.4 Hz, 1H, 4-C*H*=), 5.18 (d, J = 1.3 Hz, 1H, 5-CH_2=), 5.15 (dd, J = 9.7, 1.9 Hz, 1H, 5-CH_2=), 4.99 (d, J = 12.5 Hz, 1H, 2′-C*H*=), 4.99 (sept, J = 6.3 Hz, 1H, O*i*PrC*H*), 4.74 (d^{AB}, J = 11.9 Hz, 1H, 2‴-CH_2Ph), 4.70 (d^{AB}, J = 12.0 Hz, 1H, 2‴-CH_2Ph), 4.48 (d^{AB}, J = 11.9 Hz, 1H, 3″-CH_2Ph), 4.42 (d^{AB}, J = 11.7 Hz, 1H, 3″-CH_2Ph), 3.71 (dd^{AB}, J = 9.6, 4.1 Hz, 1H, 3″-CH_2OBn), 3.65 (s, 1H), 3.57 (dd^{AB}, J = 9.4, 7.5 Hz, 1H, 3″-CH_2OBn), 2.75 − 2.65 (m, 1H, 3-C*H*), 1.23 (d, J = 6.2 Hz, 3H, O*i*Pr−CH_3), 1.17 (d, J = 6.2 Hz, 3H, O*i*PrCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0 (1-*C*), 148.4 (2″-*C*H=), 138.2 (*C*-Ar), 136.7 (*C*-Ar), 135.2 (4-*C*H=), 128.5 (2 × *C*H-Ar), 128.3 (2 × *C*H-Ar), 127.9 (*C*H-Ar), 127.6 (2 × *C*H-Ar), 127.5 (*C*H-Ar,), 127.4 (2 × *C*H-Ar), 118.9 (5-*C*H_2=), 105.3 (2′-*C*H=), 77.1 (2-*C*), 73.2 (2‴-*C*H_2Ph), 71.6 (3″-*C*H_2Ph), 70.0 (O*i*Pr*C*H), 69.8 (3′-*C*H_2), 51.6 (3-*C*H), 21.6 (2 × O*i*Pr*C*H_3); IR (in substance) ν 3500, 3070−3030, 2980−2870, 1720, cm^{-1}. Anal. Calcd for $C_{25}H_{30}O_5$: C, 73.15; H, 7.37. Found: C, 73.09; H, 7.80.

Ester (±)-*syn*-24. To an ice-cooled solution of the benzyl enol ether **16** (2.36 g, 5.8 mmol, 1.0 equiv) in THF (0.5 mL/mmol **16**) was added aq HCl (1.94 M, 4.3 mL, 8.4 mmol, 1.5 equiv) and the mixture stirred for 72 h at ambient temperature. The reaction mixture was then quenched with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude aldehyde that was used without further purification: R_f 0.44 heptane/ethyl acetate 1/1.

To a solution of the crude aldehyde (5.8 mmol, 1.0 equiv) in *t*-BuOH (10 mL/mmol aldehyde) and 2-methyl-2-butene (10 mL/mmol aldehyde) was added a solution of $NaClO_2$ (5.20 g, 57.5 mmol, 10.0 equiv) and $NaH_2PO_4 \cdot H_2O$ (5.55 g, 40.2 mmol, 7.0 equiv) in water (20 mL/mmol aldehyde). The reaction mixture was stirred at ambient temperature for 12 h, diluted with water, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Purification by flash chromatography (heptane/ethyl acetate 10/1 to 1/2) provided the acid (1.79 g, 5.3 mmol, 93%): R_f 0.09 heptane/ethyl acetate 1/1.

To an ice-cooled solution of the acid (1.79 g, 5.3 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL/mmol acid) were added DMAP (32 mg, 0,3 mmol, 0.05 equiv), DCC (1.21 g, 5.9 mmol, 1.1 equiv), and MeOH (1 mL, 15.9 mmol, 2.0 equiv). The resulting suspension was stirred for 30 min at ambient temperature. The precipitate was then removed by filtration and washed with CH_2Cl_2, and the solvent was evaporated under reduced pressure. Flash chromatography (heptane/ethyl acetate 10/1 to 5/1) afforded of the ester **24** (1.5 g, 4.3 mmol, 81%): R_f 0.32 heptane/ethyl acetate 1/1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.24 (m, 5H), 5.77 (ddd, J = 16.8, 10.3, 10.3 Hz, 1H), 5.15 (s, 1H), 5.13 (dd, J = 8.7, 1.6 Hz, 1H), 5.04 (sept, J = 6.3 Hz, 1H), 4.50 (d^{AB}, J = 12.0 Hz, 1H), 4.45 (d^{AB}, J = 11.7 Hz, 1H), 4.00 (s, 1H), 3.70 (dd^{AB}, J = 9.6, 6.5 Hz, 1H), 3.64 (s, 3H), 3.52 (dd^{AB}, J = 9.8, 5.4 Hz, 1H), 2.94 (d^{AB}, J = 16.8 Hz, 1H), 2.86 (d^{AB}, J = 16.1 Hz, 1H), 2.67−2.61 (m, 1H), 1.29 (d, J = 6.0 Hz, 3H), 1.21 (d, J = 6.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4 (C), 171.1 (C), 137.9 (C), 134.5 (CH), 128.3 (2 × CH), 127.7 (2 × CH), 127.6 (CH), 119.0 (CH_2), 76.1 (C), 73.3 (CH_2), 69.9 (CH_2), 52.4 (CH or CH_3), 51.7 (CH or CH_3), 42.4 (CH_2), 21.7 (CH_3), 21.6 (CH_3); IR (in substance) ν 3480−2980, 2920−2835, 1740 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.37. Found: C, 65.17; H, 7.65.

Silyl Ether (±)-*syn*-25. To an ice-cooled solution of the ester **24** (1.08 g, 3.1 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL/mmol **24**) were added 2,6-lutidine (1.4 mL, 12.4 mmol, 4.0 equiv) and TBSOTf (2.45 g, 9.3 mmol, 3.0 equiv). The resulting mixture was stirred at ambient temperature until TLC indicated complete consumption of the starting material (∼3 h). The reaction was quenched with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography (heptane/ethyl acetate 20/1 to 10/1) afforded 1.39 g (3.0 mmol, 97%) of silyl ether **25**: R_f 0.79 heptane/ethyl acetate 1/1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21−7.04 (m, 5H), 5.61 (ddd, J = 16.9, 10.2, 10.2 Hz, 1H), 4.97 (d, J = 1.9 Hz, 1H), 4.94 (dd, J = 10.2, 1.8 Hz, 1H), 4.80 (sept, J = 6.3 Hz, 1H), 4.30 (s, 2H), 3.63 (dd^{AB}, J = 5.4, 9.6 Hz, 1H), 3.44 (s, 3H), 3.28 (dd^{AB}, J = 6.5, 9.7 Hz, 1H), 2.81 (d^{AB}, J = 15.3 Hz, 1H), 2.68 (d^{AB}, J = 15.3 Hz, 1H), 2.61−2.51 (m, 1H), 1.06 (d, J = 6.5 Hz, 3H), 1.02 (d, J = 6.5 Hz, 3H), 0.64 (s, 9H), 0.00 (s, 3H), −0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9 (C), 170.4 (C), 138.1 (C), 135.7 (CH), 128.3 (2 × CH), 127.7 (2 × CH), 127.6 (CH), 118.5 (CH_2), 79.8 (C), 73.1 (CH_2), 69.5 (CH_2), 69.1 (CH), 53.5 (CH or CH_3), 51.5 (CH or CH_3), 43.9 (CH_2), 26.0 (3 × CH_3), 21.8 (CH_3), 21.7 (CH_3), 18.9 (C), −2.5 (CH_3), −2.9 (CH_3); IR (in substance) ν 2975−2855, 1745 cm^{-1}. Anal. Calcd for $C_{25}H_{40}O_6Si$: C, 64.62; H, 8.68. Found: C, 64.68; H, 8.85.

C_{15}-Alcohol 30a. To a stirred solution of 1,3-dithiane (**27**) (0.76 g, 6.3 mmol, 1.0 equiv) in THF (2 mL/mmol **27**) was added *n*-BuLi (2.45 M in hexane, 2.7 mL, 6.6 mmol, 1.05 equiv) at −78 °C and the mixture stirred for 1 h at −5 °C. 1-Bromoheptane (**28a**) (1.01 mL, 6.4 mmol, 1.01 equiv) was added at −78 °C, and the reaction mixture was allowed to warm to ambient temperature over 3 h. The reaction was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Flash chromatography (heptane) afforded dithiane **46a** (1.27 g, 5.8 mmol, 93%) as a pale yellow oil: R_f 0.47 heptane/ethyl acetate 20/1.

To a stirred solution of the monoalkylated dithiane (1.31 g, 6.0 mmol, 2.0 equiv) in HMPA (2.9 mL, 16 mmol, 8 equiv) and THF (7.5 mL/mmol **29**) was added *t*-BuLi (1.5 M in pentane, 12.0 mL, 18.0 mmol, 3 equiv) at −78 °C. Within 1 min, a cooled solution (−78 °C) of iodide **29** (1.92 g, 4.0 mmol, 1.0 equiv) in THF (5 mL) was added via cannula. The reaction mixture was stirred for 1 h at −78 °C and then quenched with saturated aq NH_4Cl and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic phases were dried over $MgSO_4$ and concentrated.

The resulting crude product was diluted with THF (5 mL/mmol **29**) and solid tetrabutylammonium fluoride (1.27 g, 4.0 mmol, 1 equiv) was added. After the mixture was stirred for 1 h at rt, the reaction was quenched with saturated aq $NaHCO_3$

and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Flash chromatography (heptane/ethyl acetate 10/1 to 5/1) afforded alcohol **30a** (1.22 g, 3.7 mmol, 92%) as a colorless oil: R_f 0.52 heptane/ethyl acetate 1/1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (t, J = 6.5 Hz, 2H), 2.84−2.73 (m, 4H), 1.99−1.89 (m, 2H), 1.89−1.79 (m, 4H), 1.63−1.20 (series of m, 20H), 0.87 (t, J = 6.7 Hz, 3H) no OH-resonance observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.0 (CH_2), 53.4 (C), 38.2 (2 × CH_2), 32.8 (CH_2), 31.8 (CH_2), 29.8 (2 × CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.0 (2 × CH_2), 25.7 (CH_2), 25.6 (CH_2), 24.1 (CH_2), 24.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3); IR (in substance) ν 3345, 2925−2855 cm^{-1}. Anal. Calcd for $C_{18}H_{36}OS_2$: C, 65.00; H, 10.91; S, 19.28. Found: C, 65.28; H, 11.15; S, 18.95.

C_{17}-Alcohol 30b. As described in the preceding paragraph, consecutive treatment of 1,3-dithiane (**27**) (3.0 g, 25.0 mmol) with *n*-BuLi (2.36 M in hexane, 11.1 mL, 26.2 mmol) and 1-bromononane **28b** (5.3 g, 25.5 mmol) afforded the monoalkylated dithiane (5.97 g, 24.2 mmol, 97%) as a pale yellow oil: R_f 0.36 heptane/ethyl acetate 20/1. The monoalkylated dithiane (1.12 g, 4.6 mmol) in HMPA (2.2 mL, 12.1 mmol) and THF was then treated with *t*-BuLi (1.5 M in pentane, 6.0 mL, 9.0 mmol) and iodide **29** (1.46 g, 3.0 mmol). The crude product was subjected to tetrabutylammonium fluoride (0.96 g, 3.0 mmol). Flash chromatography provided **30b** (0.94 g, 2.6 mmol, 86%) as a colorless oil: R_f 0.49 heptane/ethyl acetate 1/1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.56 (dt, J = 5.7, 5.7 Hz, 2H), 2.74−2.66 (m, 4H), 1.90−1.80 (m, 2H), 1.79−1.70 (m, 4H), 1.53−1.09 (series of m, 24H), 0.79 (t, J = 6.7 Hz, 3H) no HO-resonance observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.0 (CH_2), 53.4 (C), 38.2 (CH_2), 32.8 (CH_2), 31.9 (CH_2), 29.81 (CH_2), 29.78 (CH_2), 29.54 (CH_2), 29.47 (CH_2), 29.3 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 24.1 (CH_2), 24.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3) (several overlapping signals between 38.2 and 22.7, total number (CH_2): 18); IR (in substance) ν 3345, 2925−2850 cm^{-1}. Anal. Calcd for $C_{20}H_{40}OS_2$: C, 66.60; H, 11.18; S, 17.78. Found: C, 66.26; H, 11.38; S, 17.58.

Phenyl-1*H*-tetrazole 31a. An icecooled solution of alcohol **30a** (1.44 g, 4.3 mmol, 1.0 equiv) in THF (1 mL/mmol **30a**) was treated with PPh_3 (1.35 g, 5.2 mmol, 1.2 equiv), 1-phenyl-1*H*-tetrazole-5-thiol (1.15 g, 6.5 mmol, 1.5 equiv), and diisopropyl azodicarboxylate (1.13 g, 5.6 mmol, 1.3 equiv). After 10 min of stirring, saturated aq $NaHCO_3$ (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Flash chromatography (heptane/ethyl acetate 10/1) afforded tetrazole **31a** (2.1 g, 4.3 mmol, 100%) as a yellow oil: R_f 0.33 heptane/ethyl acetate 1/1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63−7.50 (m, 5H), 3.39 (t, J = 7.5 Hz, 2H), 2.88−2.75 (m, 4H), 1.99−1.89 (m, 2H), 1.88−1.78 (m, 6H), 1.67−1.17 (series of m, 18H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5 (C), 133.8 (C), 130.1 (CH), 129.8 (2 × CH), 123.9 (2 × CH), 53.3 (C), 38.2 (CH_2), 38.1 (CH_2), 33.3 (CH_2), 31.8 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 26.0 (CH_2), 25.6 (CH_2), 24.1 (CH_2), 24.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3); IR (in substance) ν 3055, 2925−2855 cm^{-1}. Anal. Calcd for $C_{25}H_{40}N_4S_3$: C, 60.93; H, 8.18; N, 11.37; S, 19.52. Found: C, 61.15; H, 8.40; N, 11.63; S, 19.67.

Phenyl-1*H*-tetrazole 31b. As described for tetrazole **31a**, alcohol **30b** (905 mg, 2.5 mmol, 1 equiv) was treated with PPh_3 (787 g, 3.0 mmol, 1.2 equiv), 1-phenyl-1*H*-tetrazole-5-thiol (668 mg, 3.8 mmol, 1.5 equiv), and diisopropylazodicarboxylate (657 mg, 3.3 mmol, 1.3 equiv). Flash chromatography provided the tetrazole **31b** (1.28 g, 2.5 mmol, 98%) as a yellow oil: R_f 0.53 heptane/ethyl acetate 1/1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.50 (m, 5H), 3.38 (t, J = 7.3 Hz, 2H), 2.83−2.73 (m, 4H), 1.98−1.88 (m, 2H), 1.87−1.76 (m, 6H), 1.52−1.18 (series of m, 22H), 0.87 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.4 (C), 142.6 (C), 130.0 (CH), 129.7 (2 × CH), 123.9 (2 × CH), 53.4 (C), 38.3 (CH_2), 38.2 (CH_2), 33.3 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.53 (CH_2), 29.47 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 26.0 (2 × CH_2), 25.6 (CH_2), 24.1 (CH_2), 24.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3); IR (in substance) ν 2925−2850 cm^{-1}. Anal. Calcd for $C_{27}H_{44}N_4S_3$: C, 62.26; H, 8.51; N, 10.76; S, 18.47. Found: C, 62.32; H, 8.59; N, 10.96; S, 18.45.

Sulfone 32a. To a solution of 1,3-dithiane **31a** (1.00 g, 2.0 mmol, 1.0 equiv) in acetone/water (v/v = 99/1, 8 mL/mmol of the dithiane) were added $CuCl_2$ (546 mg, 4.1 mmol, 2.0 equiv) and CuO (646 mg, 8.1 mmol, 4.0 equiv). The mixture was stirred at rt for 45 min and filtered through a Celite pad. The pad was washed with Et_2O, and the combined organic phases were concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (75 mL) and extracted with saturated aq $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated. Flash chromatography (heptane/ethyl acetate 10/1) afforded the corresponding ketone (701 mg, 1.7 mmol, 86%) as pale yellow oil: R_f 0.44 heptane/ethyl acetate 1/1.

The ketone (1.63 g, 4.1 mmol, 1.0 equiv) in ethanol (10 mL/mmol ketone) was cooled to 0 °C and treated with $(NH_4)_6Mo_7O_{24}\cdot H_2O$ (501 mg, 0.4 mmol, 0.1 equiv) in hydrogen peroxide (30%, 4.5 mL, 41 mmol, 10.0 equiv). The resultant suspension was stirred at ambient temperature for 24 h and then added to brine (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Flash chromatography (heptane/ethyl acetate 3/1) afforded the corresponding sulfone (1.74 g, 4.1 mmol, 99%) as pale yellow oil: R_f 0.29 heptane/ethyl acetate 1/1.

A solution of the sulfone (1.74 g, 4.0 mmol, 1.0 equiv) and 1,2-bis-trimethylsilyloxyethane (2.48 g, 12.0 mmol, 3.0 equiv) in CH_2Cl_2 (2 mL/mmol sulfone) was cooled to −5 °C and treated with TMSOTf (88 mg, 0.4 mmol, 0.1 equiv). The mixture was stirred for 24 h at −5 °C. The reaction was then quenched by the addition of pyridine (1 mL/mmol sulfone) and added to saturated aq $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Flash chromatography (heptane/ethyl acetate 5/1) provided ketal **32a** (1.91 g, 4.0 mmol, 98%) as a pale yellow oil: R_f 0.29 heptane/ethyl acetate 1/1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.58 (m, 5H), 3.91 (s, 4H), 3.76−3.67 (m, 2H), 2.00−1.88 (m, 2H), 1.62−1.20 (series of m, 22H), 0.88 (br t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5 (C), 133.0 (C), 131.4 (CH), 129.7 (2 × CH), 125.0 (2 × CH), 111.7 (C), 64.9 (2 × CH_2), 56.0 (CH_2), 37.2 (CH_2), 37.0 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.9 (CH_2), 28.0 (CH_2), 23.9 (CH_2), 23.6 (CH_2), 22.6 (CH_2), 21.9 (CH_2), 14.1 (CH_3); IR (in substance) ν 2925−2855 cm^{-1}. Anal. Calcd for $C_{24}H_{38}N_4O_4S$: C, 60.22; H, 8.00; N, 11.71; S, 6.70. Found: C, 60.27; H, 8.13; N, 11.83; S, 6.38.

Sulfone 32b. As described for the synthesis of ketale **32a** in the preceding paragraph, 1,3-dithiane **31b** (1.24 g, 2.4 mmol, 1 equiv) was treated with $CuCl_2$ (645 mg, 4.8 mmol, 2 equiv) and CuO (760 mg, 9.2 mmol, 4 equiv). Flash chromatography (heptane/ethyl acetate 10/1) provided the corresponding ketone (876 mg, 2.0 mmol, 85%) as a pale yellow oil: R_f 0.36 heptane/ethyl acetate 1/1. The ketone (840 mg, 1.9 mmol) was then treated with $(NH_4)_6Mo_7O_{24}\cdot H_2O$ (251 mg, 0.19 mmol, 0.1 equiv) in hydrogen peroxide (30%, 2.30 mL, 20.3 mmol, 10,7 equiv). Flash chromatography (heptane/ethyl acetate 5/1) afforded the corresponding sulfone **51b** (766 mg, 1.7 mmol, 85%) as a pale yellow oil: R_f 0.56 heptane/ethyl acetate 1/1. The sulfone (660 mg, 1.4 mmol) was then subjected to 1,2-bis-trimethylsilanyloxyethane (883 mg, 4.3 mmol, 3.1 equiv) and TMSOTf (32 mg, 0.14 mmol, 0.1 equiv). Flash chromatography (heptane/ethyl acetate 5/1) afforded ketal **32b** (670 mg, 1.3 mmol, 92%) as a pale yellow oil: R_f 0.61 heptane/ethyl acetate 1/1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69−7.57 (m, 5H), 3.91 (s, 4H), 3.73−3.70 (m, 2H), 1.97−1.91 (m, 2H), 1.59−1.22 (series of m, 26H), 0.86 (br t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5 (C), 133.1 (C), 131.4 (CH), 129.7 (2 × CH), 125.1 (2 × CH), 111.8 (C), 64.9 (2 × CH_2), 56.0 (CH_2), 37.2 (CH_2), 37.0 (CH_2),

31.9 (CH_2), 29.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 28.0 (CH_2), 23.9 (CH_2), 23.6 (CH_2), 22.6 (CH_2), 21.9 (CH_2), 14.1 (CH_3); IR (in substance) ν 2925−2855, 1710 cm^{-1}. Anal. Calcd for $C_{26}H_{42}N_4O_4S$: C, 61.63; H, 8.35; N, 11.06;, S, 6.33. Found: C, 61.85; H, 8.15; N, 11.27; S, 6.39.

Sulfone 32c. As described for tetrazole **31a**, pentadecanol (914 mg, 4.0 mmol, 1 equiv) was treated with PPh_3 (1.26 g, 4.8 mmol, 1.2 equiv), 1-phenyl-1*H*-tetrazole-5-thiol (1.07 g, 6.0 mmol, 1.5 equiv), and diisopropyl azodicarboxylate (1.05 g, 5.2 mmol, 1.3 equiv). Flash chromatography (heptane/ethyl acetate 5/1) afforded the corresponding phenyl-1*H*-tetrazole (1.55 g, 4.0 mmol, 99%) as a white solid: R_f 0.70 heptane/ethyl acetate 1/1. The tetrazole (1.55 g, 4.0 mmol, 1 equiv) was then treated with $(NH_4)_6Mo_7O_{24}\cdot H_2O$ (494 mg, 0.4 mmol, 0.1 equiv) and 30% aq hydrogen peroxide (4.4 mL, 40.0 mmol, 10 equiv) to provide sulfone **32c** (1.44 g, 3.4 mmol, 86%) as a white solid: R_f 0.68 heptane/ethyl acetate 1/1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.57 (m, 5H), 3.76−3.69 (m, 2H), 2.00−1.88 (m, 2H), 1.54−1.43 (m, 2H), 1.39−1.20 (m, 22H), 0.87 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6 (C), 133.1 (C), 131.4 (CH), 129.7 (2 × CH), 125.1 (2 × CH), 56.0 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.62 (CH_2), 29.59 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 28.1 (CH_2), 22.6 (CH_2), 21.9 (CH_2), 14.1 (CH_3) (several overlapping signals between 31.9 and 22.0, total number (CH_2): 14); IR (in substance) ν 2920−2850 cm^{-1}. Anal. Calcd for $C_{22}H_{36}N_4O_2S$: C, 62.82; H, 8.63; N, 13.32; S, 7.62. Found: C, 63.12; H, 8.71; N, 13.43; S, 7.61.

Olefin (±)-33a. Through a solution of the terminal olefin **25** (225 mg, 0.5 mmol, 1.0 equiv) in CH_2Cl_2 and MeOH (v/v = 4/1, 20 mL/mmol **25**) at −78 °C was bubbled a stream of ozone until the color of the reaction mixture turned blue (∼10 min). The excess ozone was removed by a nitrogen stream (disappearance of the blue color), and then Me_2S (0.3 mL, 4.0 mmol, 8.0 equiv) was added at −78 °C. The reaction mixture was allowed to warm to ambient temperature and stirred at this temperature until TLC indicated complete consumption of the ozonide (∼3 h). The reaction mixture was then concentrated at reduced pressure to provide the crude aldehyde (±)-syn-**26** which was used without further purification: R_f 0.23 heptane/ethyl acetate 5/1.

To a solution of the sulfon **32a** (231 mg, 0.5 mmol, 1.0 equiv) in THF (10 mL/mmol **32a**) at −78 °C was added KHMDS (0.5 M solution in THF, 0.9 mL, 0.5 mmol, 1.05 equiv), and the resulting mixture was stirred for 30 min. A cooled (−78 °C) solution of the aldehyde **26** in THF (5 mL/mmol **26**) was then added, and the mixture was warmed to ambient temperature overnight. The resulting slurry was diluted with water, the phases were separated, and the organic layer was washed with brine (2 × 10 mL), dried over $MgSO_4$, and then concentrated. Flash chromatography (heptane/ethyl acetate 20/1) afforded the olefin **33a** (292 mg, 0.4 mmol, 84%) as a colorless oil: R_f 0.38 heptane/ethyl acetate 5/1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.18 (m, 5H, C*H*-Ar), 5.44 (ddd, J = 15.0, 6.5, 6.5 Hz, 1H, 6-C*H*=), 5.24 (ddd, J = 15.2, 9.6 Hz, 1H, 5-C*H*=), 4.91 (sept, J = 6.3 Hz, 1H, O*i*PrC*H*), 4.41 (s, 2H, 4″-CH_2Ph), 3.87 (s, 4H, 13′-CH_2), 3.73 (dd^{AB}, J = 9.6, 5.4 Hz, 1H, 4′-CH_2), 3.56 (s, 3H, CO_2CH_3), 3.32 (dd^{AB}, J = 9.6, 6.3 Hz, 1H, 4′-CH_2), 2.89 (d^{AB}, J = 15.3 Hz, 1H, 2-CH_2), 2.80 (d^{AB}, J = 15.3 Hz, 1H, 2-CH_2), 2.68−2.57 (m, 1H, 4-C*H*), 1.98−1.86 (m, 2H, 7-CH_2), 1.58−1.46 (m, 4H, 12- and 14-CH_2), 1.36−1.24 (m, 18H, 8-,9-,10-,11- and 15-,16-,17-,18-,19-CH_2), 1.22 (d, J = 6.3 Hz, 3H, O*i*PrCH_3), 1.20 (d, J = 6.3 Hz, 3H, O*i*PrCH_3), 0.87 (t, J = 6.9 Hz, 3H, 20-CH_3), 0.81 (s, 9H, Si*t*BuCH_3), 0.13 (s, 3H, SiCH_3), 0.00 (s, 3H, SiCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0 (*C*O_2*i*Pr, 170.6 (*C*O_2Me), 138.3 (*C*-Ar), 134.4 (6-*C*H=), 128.3 (2 × *C*H-Ar), 127.7 (2 × *C*H-Ar), 127.5 (*C*H-Ar), 127.0 (5-*C*H=), 111.9 (13-*C*), 80.3 (3-*C*), 73.0 (4″-*C*H_2), 70.0 (4′-*C*H_2), 68.9 (*C*H*i*Pr), 64.9 (2 × 13′-*C*H_2), 52.2 (4-*C*H), 51.4 (O*C*H_3), 44.0 (2-*C*H_2), 37.1 (12- and 14-*C*H_2), 32.6 (7-*C*H_2), 31.8 (18-*C*H_2), 29.9 (*C*H_2), 29.8 (*C*H_2), 29.3 (*C*H_2), 29.23 (*C*H_2), 29.16 (*C*H_2), 26.0 (3 × Si*t*BuCH_3), 23.84 (11- or 15-*C*H_2), 23.82 (11- or 15-*C*H_2), 22.6 (*C*H_2), 21.9 (O*i*Pr*C*H_3), 21.7 (O*i*Pr*C*H_3), 19.0 (Si*t*-Bu*C*), 14.1 (20-*C*H_3), −2.4 (Si*C*H_3), −2.9 (Si*C*H_3); IR (in substance) ν 2930−2850, 1745 cm^{-1}. Anal. Calcd for $C_{41}H_{70}O_8Si$: C, 68.48; H, 9.81. Found: C, 68.63; H, 9.98.

Olefin (±)-33b. As outlined for the preparation of olefin **33a**, sulfone **32b** (182 mg, 0.36 mmol, 1.05 equiv) was treated with KHMDS (0.5 M solution in THF, 0.7 mL, 0.34 mmol, 1.0 equiv) and the aldehyde **26** (0.36 mmol, 1.05 equiv). Flash chromatography afforded olefin **33b** (190 mg, 0.3 mmol, 71%) as a colorless oil: R_f 0.35 heptane/ethyl acetate 3/1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.29 (m, 5H), 5.47 (ddd, J = 14.9, 6.6, 6.6 Hz, 1H), 5.29 (dd, J = 15.4, 9.6 Hz, 1H) 4.96 (sept, J = 6.2 Hz, 1H), 4.47 (s, 2H), 3.92 (s, 4H), 3.78 (dd^{AB}, J = 9.6, 5.7 Hz, 1H), 3.62 (s, 3H), 3.38 (dd^{AB}, J = 9.6, 6.2 Hz, 1H), 2.95 (d^{AB}, J = 15.2 Hz, 1H), 2.86 (d^{AB}, J = 15.2 Hz, 1H), 2.72−2.64 (m, 1H), 1.97 (ddd, J = 6.6, 6.5, 6.5 Hz, 2H), 1.61−1.55 (m, 4H), 1.38−1.13 (m, 22H), 1.23 (d, J = 6.1 Hz, 3H), 1.21 (d, J = 6.1 Hz, 3H), 0.82 (s, 9H), 0.88 (t, J = 6.7 Hz, 3H), 0.18 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 172.0 (C), 170.6 (C), 138.3 (C), 134.4 (CH), 128.3 (2 × CH), 127.7 (2 × CH), 127.5 (CH), 127.0 (CH), 111.9 (C), 80.3 (C), 73.0 (CH_2), 70.1 (CH_2), 68.9 (CH), 64.9 (2 × CH_2), 52.3 (CH or CH_3), 51.3 (CH or CH_3), 44.0 (CH_2), 37.2 (2 × CH_2), 34.1 (CH_2), 32.6 (CH_2), 31.9 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 29.61 (CH_2), 29.55 (CH_2), 29.3 (CH_2), 29.23 (CH_2), 29.16 (CH_2), 26.1 (3 × CH_3), 23.8 (CH_2), 22.7 (CH_2), 21.8 (CH_3), 21.7 (CH_3), 19.0 (C), 14.1 (CH_3), −2.4 (CH_3), −2.9 (CH_3); IR (in substance) ν 2955−2855, 1745 cm^{-1}. Anal. Calcd for $C_{43}H_{74}O_8Si$: C, 69.13; H, 9.98, Found: C, 69.37; H, 10.03.

Olefin (±)-33c. Analogous to the procedure for the preparation of olefin **33a**, sulfon **32c** (284 mg, 0.7 mmol, 1.35 equiv) was treated with KHMDS (0.5 M solution in THF, 1.3 mL, 0.7 mmol, 1.3 equiv) and the aldehyde **26** (0.5 mmol, 1.0 equiv). Flash chromatography afforded olefin **33c** (232 mg, 0.35 mmol, 70%) as a colorless oil: R_f 0.56 heptane/ethyl acetate 5/1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.23 (m, 5H), 5.50 (dt, J = 15.1, 6.2 Hz, 1H), 5.31 (dd, J = 15.3, 9.6 Hz, 1H), 4.95 (sept, J = 6.2 Hz, 1H), 4.46 (s, 2H), 3.79 (dd^{AB}, J = 9.6, 5.8 Hz, 1H), 3.61 (s, 3H), 3.39 (dd^{AB}, J = 9.5, 6.3 Hz, 1H), 2.95 (d^{AB}, J = 15.1 Hz, 1H), 2.86 (d^{AB}, J = 15.1 Hz, 1H), 2.69 (ddd, J = 9.7, 5.9 Hz, 1H), 1.97 (dt, J = 6.8, 6.8 Hz, 2H), 1.40−1.16 (m, 30H), 0.88 (t, J = 6.9 Hz, 3H), 0.81 (s, 9H), 0.17 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9 (C), 170.5 (C), 138.4 (C), 134.4 (CH), 128.2 (2 × CH), 127.7 (2 × CH), 127.4 (CH), 127.0 (CH), 80.3 (C), 73.0 (CH_2), 70.2 (CH_2), 68.9 (CH), 52.3 (CH or CH_3), 51.2 (CH or CH_3), 43.9 (CH_2), 32.6 (CH_2), 31.9 (CH_2), 29.63 (CH_2), 29.60 (CH_2), 29.58 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.1 (3 × CH_3), 22.6 (CH_2) (several overlapping signals between 44.0 and 22.7, total number (CH_2): 16), 21.8 (CH_3), 21.6 (CH_3), 18.9 (C), 14.0 (CH_3), −2.5 (CH_3), −2.9 (CH_3); IR (in substance) ν 2925−2855, 1745 cm^{-1}. Anal. Calcd for $C_{39}H_{68}O_6Si$: C, 70.86; H, 10.37. Found: C, 70.63; H, 10.62.

Acid (±)-35a. To a solution of the olefin **33a** (186 mg, 0.26 mmol, 1.0 equiv) in DMF (20 mL/mmol **33a**) was added palladium on activated carbon (Pd/C) (110 mg, 50 mg/0.1 mmol). The flask was then equipped with a three way faucet connected to a hydrogen balloon. The suspension was carefully degassed, recharged with hydrogen, and vigorously stirred until TLC indicated complete consumption of the starting material (R_f 0.56 heptane/ethyl acetate 1/1). The Pd/C catalyst was removed by filtration and the solvents were evaporated under *high vacuum at ambient temperature* in order to avoid lactonization. The crude alcohol **34a** (R_f 0.38 heptane/ethyl acetate 1/1) was immediately used for the next reaction due to its susceptibility to lactonization.

To a solution of the crude alcohol **34a** in CH_2Cl_2 (20 mL/mmol **34a**) were added freshly activated 4 Å molecular sieves (200 mg), *N*-methylmorpholine-*N*-oxide (NMO) (61 mg, 0.51 mmol, 2.0 equiv), and tetrapropylammoniumperuthenate (TPAP) (12.7 mg, 0.03 mmol, 0.1 equiv). The resulting black suspension was stirred for 20 min at rt and then filtrated through a plug of silica gel (washing with heptane/ethyl acetate 20/1). The solvents were then evaporated under reduced

pressure, and the crude aldehyde **53a** (R_f 0.59 heptane/ethyl acetate 1/1) was dissolved in *t*-BuOH (20 mL/mmol **33a**) and 2-methyl-2-butene (4 mL/mmol **33a**) to which a solution of $NaClO_2$ (235 mg, 2.6 mmol, 10.0 equiv) and $NaH_2PO_4 \cdot H_2O$ (248 mg, 1.8 mmol, 7.0 equiv) in water (4 mL/mmol **33a**) was added. The suspension was vigorously stirred at ambient temperature for 12 h, diluted with water, and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated. Flash chromatography (heptane/ethyl acetate 10/1 to 5/1 to 1/1) afforded the acid **35a** (134 mg, 0.21 mmol, 81%) as pale yellow oil: R_f 0.29 heptane/ethyl acetate 1/1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50−5.42 (m, 2H), 4.94 (sept, J = 6.2 Hz, 1H), 3.82 (s, 4H), 3.55 (s, 3H), 3.36 (d, J = 8.3 Hz, 1H), 2.95 (d^{AB}, J = 15.2 Hz, 1H), 2.72 (d^{AB}, J = 15.2 Hz, 1H), 1.91 (ddd, J = 7.0, 6.7, 6.7 Hz, 2H), 1.51−1.49 (m, 4H), 1.27−1.14 (m, 24H), 0.91 (t, J = 6.6 Hz, 3H), 0.75 (s, 9H), 0.11 (s, 3H), 0.00 (s, 3H) no CO_2H-resonance observed; ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0 (C), 170.7 (C), 170.1 (C), 137.1 (C), 122.7 (CH), 111.9 (C), 79.7 (C), 69.7 (CH), 64.9 (2 × CH_2), 58.3 (CH or CH_3), 51.7 (CH or CH_3), 43.4 (CH_2), 37.14 (CH_2), 37.08 (CH_2), 32.5 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 25.9 (3 × CH_3), 23.84 (CH_2), 23.76 (CH_2), 22.6 (CH_2), 21.8 (CH_3), 21.6 (CH_3), 18.8 (C), 14.1 (CH_3), −2.7 (CH_3), −2.9 (CH_3); IR (in substance) ν 2930−2855, 1750, 1715 cm^{-1}. Anal. Calcd for $C_{34}H_{62}O_9Si$: C, 63.52; H, 9.72. Found: C, 63.45; H, 9.41.

Acid (±)-35b. As described for the preparation of the acid **35a**, olefin **33b** (79 mg, 0.11 mmol, R_f 0.67 heptane/ethyl acetate 1/1) was debenzylated to afford the corresponding alcohol **34b** (R_f 0.50 heptane/ethyl acetate 1/1). The alcohol was then treated with NMO (25 mg, 0.21 mmol) and TPAP (4 mg, 0.01 mmol). The resulting crude aldehyde (R_f 0.62 heptane/ethyl acetate 1/1) was oxidized with $NaClO_2$ (96 mg, 1.1 mmol) and $NaH_2PO_4 \cdot H_2O$ (101 mg, 0.7 mmol). Flash chromatography (heptane/ethyl acetate 10/1 to 1/1) afforded the acid **35b** (49 mg, 0.07 mmol, 69%) as pale yellow oil: R_f 0.38 heptane/ethyl acetate 1/1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58−5.54 (m, 2H), 5.02 (sept, J = 6.3 Hz, 1H), 3.90 (s, 4H), 3.62 (s, 3H), 3.40 (d, J = 8.9 Hz, 1H), 3.04 (d, J = 15.2 Hz, 1H), 2.80 (d, J = 15.3 Hz, 1H) 2.01−1.97 (m, 2H), 1.58−1.53 (m, 4H), 1.35−1.22 (m, 28H), 0.82 (s, 9H), 0.86 (t, J = 6.9 Hz, 3H), 0.18 (s, 3H), 0.07 (s, 3H) no CO_2H-resonance observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2 (C), 170.7 (C), 170.1 (C), 137.1 (CH), 122.7 (CH), 111.9 (C), 79.7 (C), 69.7 (CH), 64.9 (2 × CH_2), 58.4 (CH or CH_3), 51.6 (CH or CH_3), 43.4 (CH_2), 37.2 (CH_2), 37.1 (CH_2), 32.5 (CH_2), 31.9 (CH_2), 30.0 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 25.9 (3 × CH_3), 23.8 (CH_2), 23.7 (CH_2), 22.7 (CH_2), 21.8 (CH_3), 21.6 (CH_3), 18.8 (C), 14.1 (CH_3), −2.7 (CH_3), −2.9 (CH_3); IR (in substance) ν 2925−2855, 1745, 1710 cm^{-1}. Anal. Calcd for $C_{36}H_{66}O_9Si$: C, 64.49; H, 9.92. Found: C, 64.18; H, 9.92.

Acid (±)-35c. As described for the preparation of the acid **35a**, olefin **33c** (351 mg, 0.53 mmol, 1 equiv) (R_f 0.71 heptane/ethyl acetate 1/1) was debenzylated to provide the corresponding alcohol (R_f 0.50 heptane/ethyl acetate 1/1) that was treated with NMO (130 mg, 1.1 mmol) and TPAP (26 mg, 0.05 mmol). The resulting crude aldehyde **53c** (R_f 0.59 heptane/ethyl acetate 1/1) was subjected to $NaClO_2$ (160 mg, 5.3 mmol) and $NaH_2PO_4 \cdot H_2O$ (130 mg, 3.7 mmol). Flash chromatography (heptane/ethyl acetate 10/1 to 1/1) afforded the acid **35c** (218 mg, 0.37 mmol, 70%) as a pale yellow oil: R_f 0.35 heptane/ethyl acetate 1/1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (dt, J = 15.3, 6.8 Hz, 1H), 5.51 (dd, J = 15.3, 9.7 Hz, 1H), 5.01 (sept, J = 6.2 Hz, 1H), 4.37 (br s, 1H), 3.67 (s, 3H), 3.34 (d, J = 9.8 Hz, 1H), 3.02 (d^{AB}, J = 16.1 Hz, 1H), 2.83 (d^{AB}, J = 15.3 Hz, 1H), 2.02 (td, J = 6.6, 6.6 Hz, 2H), 1.29−1.21 (m, 30H), 0.88 (t, J = 7.1 Hz, 3H), 0.84 (s, 9H), 0.20 (s, 3H), 0.09 (s, 3H) no CO_2H-resonance observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1 (C), 170.6 (C), 170.0 (C), 137.3 (CH), 122.6 (CH), 79.7 (C), 69.7 (CH), 58.2 (CH or CH_3), 51.5 (CH or CH_3), 43.4 (CH_2), 32.5 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 25.9 (3 × CH_3), 22.6 (CH_2), (several overlapping signals between 43.4 and 22.6, total number of (CH_2): 14) 21.7 (CH_3), 21.6 (CH_3), 18.8 (C), 14.0 (CH_3), −2.7 (CH_3), −2.9 (CH_3); IR (in substance) ν 2980−2855, 1748, 1710 cm^{-1}. Anal. Calcd for $C_{32}H_{60}O_7Si$: C, 65.71; H, 10.34. Found: C, 65.98; H, 10.53.

β-Hydroxy Acid (±)-37a. To a solution of the acid **35a** (60 mg, 0.09 mmol, 1.0 equiv) in THF (4 mL/0.1 mmol **35a**) was added HF·pyridine (0.15 mL, 0.15 mL/0.1 mmol **35a**) at 0 °C. The reaction mixture was stirred overnight at 45 °C. If TLC indicated incomplete consumption of the starting material, additional HF·pyridine (0.15 mL, 0.15 mL/0.1 mmol **35a**) was added and stirring was continued for another 3 h at 45 °C. The reaction was quenched by the careful addition of saturated aq $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography (heptane/ethyl acetate 1/1 to pure ethyl acetate) afforded the β-hydroxy acid **37a** (22 mg, 0.045 mmol, 51%) as a colorless oil: R_f 0.21 ethyl acetate; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (ddd, J = 15.1, 6.6, 6.6 Hz, 1H), 5.52 (dd, J = 15.3, 9.6 Hz, 1H), 5.08 (sept, J = 6.3 Hz, 1H), 4.25 (s, 1H (OH)), 3.66 (s, 3H), 3.32 (d, J = 9.6 Hz, 1H), 3.00 (d^{AB}, J = 16.3 Hz, 1H), 2.83 (d^{AB}, J = 16.3 Hz, 1H), 2.37 (t, J = 7.5 Hz, 4H), 2.00 (ddd, J = 6.9, 6.8, 6.8 Hz, 2H), 1.57−1.50 (m, 4H), 1.35−1.23 (m, 20H), 0.86 (t, J = 6.9 Hz, 3H) no CO_2H-resonance observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8 (C), 173.8 (C), 171.7 (C), 170.3 (C), 138.1 (CH), 121.2 (CH), 75.7 (C), 70.8 (CH), 56.9 (CH or CH_3), 51.9 (CH or CH_3), 42.8 (CH_2), 42.7 (CH_2), 41.6 (CH_2), 32.4 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 23.9 (CH_2), 23.7 (CH_2), 22.6 (CH_2), 21.7 (CH_3), 21.5 (CH_3), 14.1 (CH_3); IR (in substance) ν 3495, 2930−2855, 1740, 1715 cm^{-1}. Anal. Calcd for $C_{26}H_{44}O_8$: C, 64.44; H, 9.15. Found: C, 64.50; H, 9.18.

β-Hydroxy Acid (±)-37b. As described for the β-hydroxy acid **37a**, the acid **35b** (55 mg, 0.08 mmol) was treated with HF·pyridine (0.12 mL). Flash chromatography (heptane/ethyl acetate 1/1 to pure ethyl acetate) afforded the β-hydroxy acid **37b** (23 mg, 0.45 mmol, 56%) as a colorless oil: R_f 0.26 ethyl acetate; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70−5.51 (m, 2H), 5.10 (sept, J = 6.2 Hz, 1H), 4.23 (br s, 1H (OH)), 3.67 (s, 3H), 3.33 (d, J = 9.0 Hz, 1H), 3.02 (d^{AB}, J = 16.2 Hz, 1H), 2.85 (d^{AB}, J = 16.2 Hz, 1H), 2.38 (t, J = 7.4 Hz, 4H), 2.02 (ddd, J = 6.6, 6.4, 6.4 Hz, 2H), 1.61−1.50 (m, 4H), 1.31−1.24 (m, 24H), 0.88 (t, J = 6.6 Hz, 3H) no signals for COOH observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7 (C), 174.5 (C), 171.8 (C), 170.4 (C), 137.9 (CH), 121.5 (CH), 75.8 (C), 70.7 (CH), 57.0 (CH or CH_3), 51.9 (CH or CH_3), 42.8 (CH_2), 42.7 (CH_2), 41.6 (CH_2), 32.4 (CH_2), 31.8 (CH_2), 31.6 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.04 (CH_2), 28.99 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 23.9 (CH_2), 23.7 (CH_2), 22.6 (CH_2), 21.7 (CH_3), 21.5 (CH_3), 14.0 (CH_3); IR (in substance) ν 3480, 2925−2855, 1735, 1710 cm^{-1}. Anal. Calcd for $C_{28}H_{48}O_8$: C, 65.60; H, 9.44. Found: C, 65.70; H, 9.57.

β-Hydroxy Acid (±)-37c. According to the procedure for the preparation of β-hydroxy acid **37a**, acid **35c** (50 mg, 0.09 mmol) was treated with HF·pyridine (0.13 mL). Flash chromatography (heptane/ethyl acetate 1/1 to pure ethyl acetate) afforded β-hydroxy acid **37c** (31 mg, 0.07 mmol, 76%) as a colorless oil: R_f 0.23 ethyl acetate; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (ddd, J = 15.3, 6.8, 6.8 Hz, 1H), 5.51 (dd, J = 15.3, 9.7 Hz, 1H), 5.01 (sept, J = 6.2 Hz, 1H), 4.37 (br s, 1H), 3.67 (s, 3H), 3.34 (d, J = 9.8 Hz, 1H), 3.02 (d^{AB}, J = 16.1 Hz, 1H), 2.83 (d^{AB}, J = 16.1 Hz, 1H), 2.01 (td, J = 7.2, 7.2 Hz, 2H), 1.36−1.17 (m, 30 H), 0.86 (t, J = 7.1 Hz, 3H) no COOH-resonance observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8 (C), 171.5 (C), 170.2 (C), 138.6 (CH), 120.6 (CH), 75.7 (C), 71.0 (CH), 56.7 (CH or CH_3), 52.0 (CH or CH_3), 41.5 (CH_2), 32.5 (CH_2), 31.9 (CH_2), 29.68 (CH_2), 29.65 (CH_2), 29.6 (CH_2), 29.43 (CH_2), 29.36 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 22.7 (CH_2), (several overlapping signals between 41.5 and 22.7, total number of (CH_2): 14) 21.7 (CH_3), 21.5 (CH_3), 14.1 (CH_3); IR (in substance) ν 2980−2855, 1745 cm^{-1}. Anla. Calcd for $C_{26}H_{46}O_7$: C, 66.35; H, 9.85. Found: C, 66.43; H, 9.69.

Viridiofungin A ester (+)-38a and (−)-39a. To a solution of the β-hydroxy acid **37a** (27 mg, 0.06 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL/mmol **37a**) were added benzotriazol-1-yloxytripyrolidinophosphonium hexaflurophosphate (PyBOP) (44 mg, 0 08 mmol, 1.5 equiv), *N*-methylmorpholine (NMM) (27 μL, 0.24 mmol, 4.4 equiv), and L-tyrosine methyl ester (16 mg, 0.08 mmol, 1.5 equiv) at ambient temperature. The resulting mixture was stirred overnight and then added to saturated aq $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Flash chromatography (heptane/ethyl acetate 1/1 to pure ethyl acetate) afforded **38a** and **39a** as a 1:1 mixture (26 mg, 0.04 mmol, 71%): R_f 0.53 ethyl acetate. The diastereomers were separated by reversed-phase HPLC. For details, see the Supporting Information.

(+)-38a: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (d, *J* = 7.7 Hz, 1H, NH), 7.01 (br s, 1H, Ph-OH), 6.94 (d, *J* = 8.5 Hz, 2H, 5′-CH-Ar), 6.77 (d, *J* = 8.5 Hz, 2H, 6′-CH-Ar), 5.55 (ddd, *J* = 15.2, 6.4, 6.4 Hz, 1H, 6-CH=), 5.23 (dd, *J* = 15.3, 9.6 Hz, 1H, 5-CH=), 5.03 (sept, *J* = 6.2 Hz, 1H, O*i*Pr-CH), 4.73 (ddd, *J* = 7.9, 7.9, 4.7 Hz, 1H, 2′-CH), 4.23 (s, 1H, 3-OH), 3.75 (s, 3H, 1′-CO_2CH_3), 3.64 (s, 3H, 1-CO_2CH_3), 3.15−3.08 (m, 1H, 3′-CH_2), 3.13 (d, *J* = 9.5 Hz, 1H, 4-CH), 3.05 (d, *J* = 16.3 Hz, 1H, 2-CH_2), 2.89 (d, *J* = 16.1 Hz, 1H, 2-CH_2), 2.91−2.86 (m, 1H, 3′-CH_2) 2.45 (t, *J* = 7.0 Hz, 2H, 12- or 14-CH_2), 2.43 (t, *J* = 7.5 Hz, 2H, 12- or 14-CH_2), 1.92−1.83 (m, 2H, 7-CH_2), 1.62−1.48 (m, 4H, 11- and 15-CH_2), 1.30−1.15 (m, 20H, O*i*Pr−CH_3, 8-,9-,10-CH_2 and 16-,17-,18-,19-CH_2), 0.86 (t, *J* = 6.9 Hz, 3H, 20-CH_3) ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 214.3 (13-C=O), 172.3 (*C*O_2*i*Pr), 171.9 (1′-*C*O_2CH_3), 170.6 (1-*C*O_2CH_3), 170.4 (*C*ONH), 155.6 (7′-COH-Ar), 137.1 (6-CH=), 130.2 (2 × 5′-CH-Ar), 127.1 (4′-C-Ar), 121.6 (5-CH=), 115.4 (2 × 6′-CH-Ar), 75.9 (3-C), 70.5 (O*i*Pr-CH), 58.0 (4-CH), 53.2 (2′-CH), 52.4 (CO_2*C*H_3), 51.8 (CO_2*C*H_3), 43.0 (12- or 14-CH_2), 42.7 (12- or 14-CH_2), 41.0 (2-CH_2), 36.5 (3′-CH_2), 32.3 (7-CH_2), 31.6 (18-CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 28.0 (CH_2), 23.9 (11- or 15-CH_2), 23.4 (11- or 15-CH_2), 22.6 (19-CH_2), 21.8 (O*i*Pr-CH_3), 21.5 (O*i*Pr-CH_3), 14.0 (20-CH_3); IR (in substance) ν 3372, 2931, 2491, 1742 cm^{-1}; $[\alpha]^{25}_D$ +52.9 (*c* 0.51, $CHCl_3$). Anal. Calcd for $C_{36}H_{55}NO_{10}$: C, 65.33; H, 8.38. Found: C, 65.06; H, 8.48.

(−)-39a: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.4 Hz, 2H, 5′-CH-Ar), 6.76 (d, *J* = 8.5 Hz, 2H, 6′-CH-Ar), 6.67 (d, *J* = 7.9 Hz, 1H, NH), 6.34 (s, 1H, Ph-OH), 5.63 (ddd, *J* = 15.2, 6.6, 6.6 Hz, H, 6-CH=), 5.49 (dd, *J* = 15.3, 9.6 Hz, 1H, 5-CH=), 5.05 (sept, *J* = 6.3 Hz, 1H, CO_2*i*Pr-CH), 4.74 (ddd, *J* = 7.1, 7.0, 5.1 Hz, 1H, 2′-CH), 4.49 (s, 1H, 3-OH), 3.72 (s, 3H, 1′-CO_2CH_3), 3.65 (s, 3H, 1-CO_2CH_3), 3.16 (d, *J* = 9.5 Hz, 1H, 4-CH), 3.09 (dd^{AB}, *J* = 14.1, 4.9 Hz, 1H, 3′-CH_2), 3.00 (dd^{AB}, *J* = 14.1, 6.8 Hz, 1H, 3′-CH_2), 2.85 (d^{AB}, *J* = 16.0 Hz, 1H, 2-CH_2), 2.68 (d^{AB}, *J* = 16.0 Hz, 1H, 2-CH_2), 2.42 (t, *J* = 7.2 Hz, 2H, 12- or 14-CH_2), 2.41 (t, *J* = 7.4 Hz, 2H, 12- or 14-CH_2), 2.01−1.92 (m, 2H, 7-CH_2), 1.59−1.48 (m, 4H, 11- and 15-CH_2), 1.34−1.18 (m, 20 H, O*i*Pr-CH_3, 8-,9-,10-CH_2 and 16-,17-,18-,19-CH_2), 0.86 (t, *J* = 6.9 Hz, 3H, 20-CH_3); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 213.4 (13-C=O), 172.2 (*C*O_2*i*Pr), 171.6 (1′-*C*O_2CH_3), 170.6 (CONH), 170.5 (1-*C*O_2CH_3), 155.4 (7′-COH-Ar), 137.8 (6-CH=), 130.4 (2 × 5′-CH-Ar), 127.3 (4′-C-Ar), 122.4 (5-CH=), 115.5 (2 × 6′-CH-Ar), 76.1 (3-C), 70.2 (O*i*Pr-CH), 57.6 (4-CH), 53.3 (2′-CH), 52.3 (CO_2*C*H_3), 51.8 (CO_2*C*H_3), 43.0 (12- or 14-CH_2), 42.7 (12- or 14-CH_2), 41.6 (2-CH_2), 36.6 (3′-CH_2), 32.5 (7-CH_2), 31.7 (18-CH_2), 29.7 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.5 (CH_2), 23.9 (11- or 15-CH_2), 23.5 (11- or 15-CH_2), 22.6 (19-CH_2), 21.7 (O*i*Pr−CH_3), 21.6 (O*i*Pr-CH_3), 14.1 (20-CH_3); IR (in substance) ν 3334, 2926, 2464, 1743 cm^{-1}; $[\alpha]^{25}_D$ −6.6 (*c* 0.15, $CHCl_3$) (lit. trimethyl ester $[\alpha]^{25}_D$ −23.0 (*c* 0.47, MeOH)). Anal. Calcd for $C_{36}H_{55}NO_{10}$: C, 65.33; H, 8.38. Found: C, 65.47; H, 8.48.

Viridiofungin A_4 Ester (+)-38b and (−)-39b. As described for the preparation of **38a** and **39a**, β-hydroxy acid **37b** (22 mg, 0.045 mmol) was treated with PyBOP (36 mg, 0.07 mmol), NMM (23 μL, 0.2 mmol), and L-tyrosine methyl ester (13 mg, 0.07 mmol). Flash chromatography (heptane/ethyl acetate 1/1 to pure ethyl acetate) afforded **38b** and **39b** as a 1:1 mixture (28 mg, 0.04 mmol, 90%): R_f 0.38 ethyl acetate. The diastereomers were separated by reversed-phase HPLC; see the Supporting Information for details.

(+)-38b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, *J* = 7.7 Hz, 1H, NH), 6.93 (d, *J* = 8.4 Hz, 2H, 5′-CH-Ar), 6.77 (d, *J* = 8.4 Hz, 2H, 6′-CH-Ar), 5.54 (ddd, *J* = 15.2, 6.4, 6.4 Hz, 1H, 6-CH=), 5.23 (dd, *J* = 15.3, 9.6 Hz, 1H, 5-CH=), 5.03 (sept, *J* = 6.3 Hz, 1H, O*i*Pr-CH), 4.73 (ddd, *J* = 7.8, 7.8, 4.7 Hz, 1H, 2′-H), 4.23 (s, 1H, 3-OH), 3.75 (s, 3H, 1′-CO_2CH_3), 3.64 (s, 3H, 1-CO_2CH_3), 3.16 (dd^{AB}, *J* = 14.3, 4.7 Hz, 1H, 3′-CH_2), 3.13 (d, *J* = 9.6 Hz, 1H, 4-H), 3.05 (d^{AB}, *J* = 16.4 Hz, 1H, 2-CH_2), 2.89 (d^{AB}, *J* = 16.4 Hz, 1 H, 2-CH_2), 2.88 (dd^{AB}, *J* = 14.4, 8.0 Hz, 1H, 3′-CH_2) 2.45 (t, *J* = 7.0 Hz, 2H, 12- or 14-CH_2), 2.42 (t, *J* = 7.6 Hz, 2H, 12- or 14-CH_2), 1.91−1.86 (m, 2H, 7-CH_2), 1.59−1.52 (m, 4H, 11- and 15-CH_2), 1.29−1.20 (m, 24H, O*i*Pr−CH_3, 8-,9-,10-CH_2 and 16-,17-,18-,19-,20-,21-CH_2), 0.86 (t, *J* = 7.0 Hz, 3H, 22-CH_3), no signal detected for 7′-OH; ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 214.2 (13-C=O), 172.3 (*C*O_2*i*Pr), 171.9 (1′-*C*O_2-CH_3), 170.6 (1-*C*O_2CH_3), 170.4 (*C*ONH), 155.6 (7′-COH), 137.1 (6-CH), 130.2 (2 × 5′-CH), 127.1 (4′-C), 121.6 (5-CH), 115.4 (2 × 6′-CH), 75.8 (3-C), 70.5 (O*i*Pr−CH), 58.0 (4-CH), 53.2 (2′-CH), 52.4 (CO_2*C*H_3), 51.8 (CO_2*C*H_3), 43.0 (12- or 14-CH_2), 42.7 (12- or 14-CH_2), 41.0 (2-CH_2), 36.5 (3′-CH_2), 32.3 (7-CH_2), 31.8 (20-CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.24 (CH_2), 29.20 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 28.0 (CH_2), 23.9 (11- or 15-CH_2), 23.4 (11- or 15-CH_2), 22.6 (21-CH_2), 21.7 (O*i*Pr−CH_3), 21.5 (O*i*Pr−CH_3), 14.1 (22-CH_3); IR (in substance) ν 3354, 2926, 2490, 2854, 1741^{-1}; $[\alpha]^{25}_D$ +22.9 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{38}H_{59}NO_{10}$: C, 66.16; H, 8.62; N, 2.03. Found: C, 66.55; H, 8.62; N, 2.01.

(−)-39b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.4 Hz, 2H, 5′-CH-Ar), 6.75 (d, *J* = 9.0 Hz, 1H, NH), 6.74 (d, *J* = 8.5 Hz, 2H, 6′-CH-Ar), 5.62 (ddd, *J* = 15.2, 6.6, 6.6 Hz, 1H, 6-CH=), 5.48 (dd, *J* = 15.3, 9.5 Hz, 1H, 5-CH=), 5.04 (sept, *J* = 6.3 Hz, 1H, CO_2*i*Pr-CH), 4.76 (ddd, *J* = 7.5, 7.4, 5.0 Hz, 1H, 2′-CH), 4.47 (s, 1H, 3-OH), 3.72 (s, 3 H, 1′-CO_2CH_3), 3.65 (s, 3H, 1-CO_2CH_3), 3.15 (d, *J* = 9.5 Hz, 1H, 4-H), 3.09 (dd^{AB}, *J* = 14.2, 4.9 Hz, 1H, 3′-CH_2), 2.98 (dd^{AB}, *J* = 14.1, 6.8 Hz, 1H, 3′-CH_2), 2.83 (d^{AB}, *J* = 16.0 Hz, 1H, 2-CH_2), 2.62 (d^{AB}, *J* = 16.0 Hz, 1H, 2-CH_2), 2.45 (t, *J* = 7.2 Hz, 2H, 12- or 14-CH_2), 2.43 (t, *J* = 7.5 Hz, 2H, 12- or 14-CH_2), 1.98−1.92 (m, 2H, 7-CH_2), 1.58−1.50 (m, 4H, 11- and 15-CH_2), 1.29−1.20 (m, 24H, O*i*Pr-CH_3, 8-,9-,10-CH_2 and 16-,17-,18-,19-,20-,21-CH_2), 0.86 (t, *J* = 6.9 Hz, 3H, 22-CH_3) no signal detected for 7′-OH; ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 213.3 (13-C=O), 172.1 (*C*O_2*i*Pr), 171.6 (1′-*C*O_2-CH_3), 170.7 (CONH), 170.5 (1-*C*O_2CH_3), 155.5 (7′-COH-Ar), 137.8 (6-CH=), 130.4 (2 × 5′-CH-Ar), 127.1 (4′-C-Ar), 122.3 (5-CH=), 115.5 (2 × 6′-CH-Ar), 76.1 (3-C), 70.2 (O*i*Pr-CH), 57.6 (4-CH), 53.3 (2′-CH), 52.3 (CO_2*C*H_3), 51.8 (CO_2*C*H_3), 43.0 (12- or 14-CH_2), 42.7 (12- or 14-CH_2), 41.5 (2-CH_2), 36.7 (3′-CH_2), 32.4 (7-CH_2), 31.8 (20-CH_2), 29.40 (CH_2), 29.36 (CH_2), 29.24 (CH_2), 29.20 (CH_2), 28.9 (2 × CH_2), 28.6 (CH_2), 23.9 (11- or 15-CH_2), 23.5 (11- or 15-CH_2), 22.6 (21-CH_2), 21.7 (O*i*Pr-CH_3), 21.5 (O*i*Pr−CH_3), 14.1 (22-CH_3); IR (in substance) ν 3346, 2926, 2854, 1741 cm^{-1}; $[\alpha]^{25}_D$ −5.1 (*c* 1.4, $CHCl_3$). Anal. Calcd for $C_{38}H_{59}NO_{10}$: C, 66.16; H, 8.62; N, 2.03. Found: C, 66.50; H, 8.78; N, 2.09.

Viridiofungin A_2 Ester (+)-38c and (−)-39c. As described for the preparation of **38a** and **39a**, β-hydroxy acid **37c** (30 mg, 0.06 mmol) was treated with PyBOP (50 mg, 0.10 mmol), NMM (31 μL, 0.28 mmol), and L-tyrosine methyl ester (19 mg, 0.10 mmol). Flash chromatography (heptane/ethyl acetate 1/1 to ethyl acetate) afforded **38c** and **39c** as a 1:1 mixture (33 mg, 0.05 mmol, 80%): R_f 0.38 ethyl acetate. The diastereomers were separated by reversed-phase HPLC; see the Supporting Information for details.

(+)-38c: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, *J* = 7.9 Hz, 1H, NH), 6.96 (d, *J* = 8.5 Hz, 2H, 5′-CH-Ar), 6.71 (d, *J* = 8.5 Hz, 2H, 6′-CH−Ar), 5.56 (ddd, *J* = 14.8, 6.6, 6.6 Hz, 1H, 6-CH=), 5.31 (dd, *J* = 15.2, 9.6 Hz, 1H, 5-CH=), 5.04 (sept, *J* = 6.2 Hz, 1H, O*i*Pr-CH), 5.02 (br s, 1H, 7′-OH), 4.77 (ddd, *J* = 7.1,

7.1, 5.6 Hz, 1H, 2′-H), 4.24 (s, 1H, 3-OH), 3.73 (s, 3H, 1′-CO_2CH_3), 3.63 (s, 3H, 1-CO_2CH_3), 3.14 (d, J = 9.6 Hz, 1H, 4-H), 3.08 (dd^{AB}, J = 14.1, 5.4 Hz, 1H, 3′-CH_2), 2.98 (d^{AB}, J = 16.3 Hz, 1H, 2-CH_2), 2.97 (dd^{AB}, J = 14.0, 7.0 Hz, 1H, 3′-CH_2), 2.87 (d^{AB}, J = 16.3 Hz, 1H, 2-CH_2), 1.96−1.91 (m, 2H, 7-CH_2), 1.27−1.21 (m, 30H, O*i*Pr-CH_3, 8-,9-,10-,11-,12-,13-,14-,15-,16-,17-,18-,19-,20-,21-CH_2), 0.87 (t, J = 6.9 Hz, 3H, 20-CH_3); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 172.3 (CO_2*i*Pr), 171.9 (1′-CO_2CH_3), 170.6 (*C*ONH or 1-CO_2CH_3), 170.5 (1-CO_2CH_3 or *C*ONH), 154.8 (7′-COH), 137.5 (6-CH), 130.4 (2 × 5′-CH), 127.8 (4′-C), 121.9 (5-CH), 115.4 (2 × 6′-CH), 75.9 (3-C), 70.5 (O*i*Pr-CH), 58.1 (4-CH), 53.1 (2′-CH), 52.3 (CO_2CH_3), 51.8 (CO_2CH_3), 41.1 (2-CH_2), 36.7 (3′-CH_2), 32.6 (7-CH_2), 31.9 (18-CH_2), 29.69 (CH_2), 29.65 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.0 (CH_2) (several overlapping signals between 29.7 and 29.0, total number of (CH_2): 15), 22.7 (19-CH_2), 21.8 (O*i*Pr-CH_3), 21.5 (O*i*Pr-CH_3), 14.1 (20-CH_3); IR (in substance) ν 3343, 2925, 2853, 1743 cm^{-1}; $[\alpha]^{25}_D$ +20.7 (*c* 0.14, $CHCl_3$). Anal. Calcd for $C_{36}H_{57}NO_9$: C, 66.74; H, 8.87. Found: C, 66.35; H, 8.87.

(−)-39c: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, J = 8.4 Hz, 2H, 5′-CH-Ar), 6.90 (d, J = 8.1 Hz, 1H, NH), 6.71 (d, J = 8.5 Hz, 2H, 6′-CH-Ar), 5.63 (ddd, J = 15.3, 6.6, 6.6 Hz, 1H, 6-CH=), 5.45 (dd, J = 15.1, 9.7 Hz, 1H, 5-CH=), 5.03 (sept, J = 6.5 Hz, 1H, CO_2*i*Pr-CH), 5.01 (br s, 1H, 7′-OH), 4.80 (ddd, J = 7.8, 7.8, 5.3 Hz, 1H, 2′-CH), 4.29 (s, 1H, 3-OH), 3.71 (s, 3H, 1′-CO_2CH_3), 3.66 (s, 3H, 1-CO_2CH_3), 3.13 (d, J = 9.4 Hz, 1H, 4-H), 3.11 (dd^{AB}, J = 13.9, 5.7 Hz, 1H, 3′-CH_2), 2.96 (dd^{AB}, J = 14.1, 7.5 Hz, 1H, 3′-CH_2), 2.81 (d^{AB}, J = 16.1 Hz, 1H, 2-CH_2), 2.52 (d^{AB}, J = 16.3 Hz, 1H, 2-CH_2), 2.01−1.94 (m, 2H, 7-CH_2), 1.27−1.21 (m, 30H, O*i*Pr-CH_3, 8-,9-,10-,11-,12-,13-,14-,15-,16-,17-,18-,19-CH_2), 0.87 (t, J = 6.9 Hz, 3H, 20-CH_3); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 172.2 (CO_2*i*Pr), 171.8 (1′-CO_2CH_3), 170.5 (CONH or 1-CO_2CH_3), 170.4 (1-CO_2CH_3 or CONH), 154.8 (7′-COH-Ar), 137.8 (6-CH=), 130.5 (2 × 5′-CH-Ar), 127.9 (4′-C−Ar), 122.0 (5-CH=), 115.5 (2 × 6′-CH-Ar), 75.9 (3-C), 70.4 (O*i*Pr-CH), 57.9 (4-CH), 53.3 (2′-CH), 52.3 (CO_2CH_3), 51.8 (CO_2CH_3), 41.3 (2-CH_2), 37.0 (3′-CH_2), 32.6 (7-CH_2), 31.9 (18-CH_2), 29.69 (CH_2), 29.65 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.0 (CH_2) (several overlapping signals between 29.7 and 29.0, total number of (CH_2): 15), 22.7 (19-CH_2), 21.7 (O*i*Pr-CH_3), 21.5 (O*i*Pr-CH_3), 14.1 (20-CH_3); IR (in substance) ν 3343, 2924, 2854, 1743 cm^{-1}; $[\alpha]^{25}_D$ −3.9 (*c* 0.19, $CHCl_3$). Anal. Calcd for $C_{36}H_{57}NO_9$: C, 66.74; H, 8.87. Found: C, 65.47; H, 8.48.

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Supporting Information Available: General experimental methods, experimental procedures and spectroscopic data for all new compounds that are not included in the Experimental Section, copies of ^{1}H and ^{13}C NMR spectra of all new compounds, and details of the assignment of the double-bond configuration of compound **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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