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Formal Total Syntheses of the (−)-Salicylihalamides A and B From D-Glucose and L-Rhamnose

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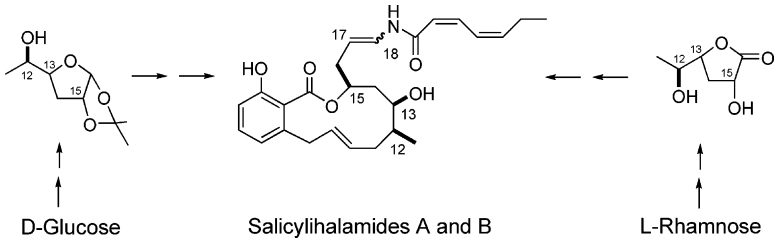
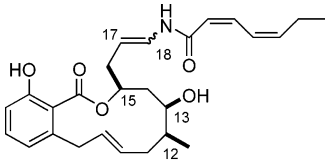


Two formal total syntheses of the (−)-salicylihalamides, based on chiral pool approaches, are reported. D-Glucose and L-rhamnose were used to prepare advanced intermediates **23** and **54**, which can be converted in three or four steps, respectively, to the target compounds. The synthesis of **23** from a known D-glucose-derivative was accomplished in 12 steps and 17% overall yield, and the synthesis of **54** from a known L-rhamnose-derivative was done in nine steps and 6% overall yield. A key step in the synthesis was a ring-closing metathesis reaction to prepare the macrocyclic ring system. It was demonstrated that the phenolic protecting group was critical for inducing the preferential formation of the desired *E* isomer. It was further shown that the protecting group at the C13 hydroxyl group had no significant influence on the *E*:*Z* ratio during the ring-closing metathesis reaction.

Introduction

The salicylihalamides A (**1**) and B (**2**), isolated in 1997 from a marine sponge of the genus *Haliclona* sp.,[1] are the most extensively studied members of a novel class of natural products that have as common structural features a salicylic acid moiety, a macrolactone, and an unusual dienyl enamide side-chain.



1 17-*E* salicylihalamide A
2 17-*Z* salicylihalamide B

Members of this class of natural products such as the oximidines,[2] the lobatamides,[3] the apicularens,[4] and the salicylihalamides displayed a striking and unique pattern of differential cytotoxicity in the NCI 60 tumor cell line assay, indicating a new mechanism of action. Further investigations revealed that these compounds inhibit mammalian V-ATPases with unprecedented specificity.[5] Prior to considering these substances as potential drug candidates, thorough investigations with respect to their exact mechanism of action are necessary. To develop a pharmacophore model, the syntheses of analogues to probe structure−activity relationships as well as biological probes to characterize the ligand binding site in the multisubunit complex of the V-ATPases are required. Novel structural features coupled with unique biological activity prompted us to undertake the total synthesis. Because the availability of the salicylihalamides from natural sources is limited, the semisynthesis of structural

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analogues from the natural product itself is restricted. Thus, obtaining the salicylihalamides synthetically is of interest. Several total syntheses of the salicylihalamides[6] and related natural products have been reported. We[7a,d−f] and others[7b,c] have employed a chiral pool approach toward the synthesis of members of this class of compounds.

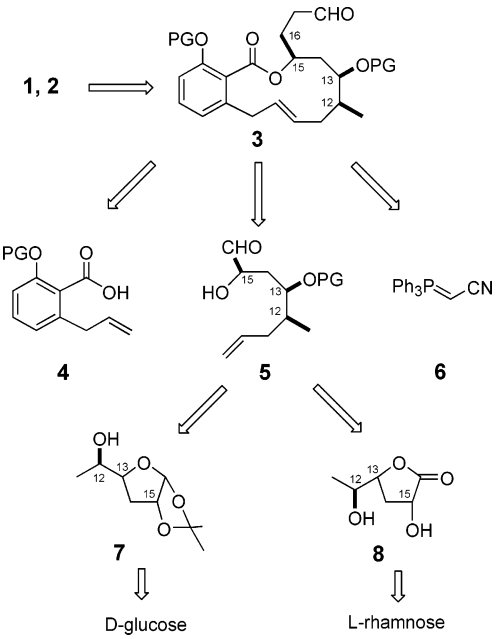
A chiral pool approach can be especially advantageous if larger amounts of the target compound have to be prepared via total synthesis. The starting materials already bearing the desired chiral centers are usually inexpensive. Moreover, enantio- or diastereoselective reactions, which might cause separation problems due to complex diastereomeric mixtures, can be avoided. In this paper, we describe the details of two efficient and high-yielding formal total syntheses of the salicylihalamides A and B, both based on a chiral pool strategy.

Results and Discussion

The initially proposed absolute stereochemistry of the salicylihalamides was revised by total synthesis[6a] at a time when we were pursuing their synthesis via a chiral pool approach, employing commercially available 1,2,5,6-diacetone-D-glucose as the starting material. We therefore first focused on the completion of the synthesis of the (+)-salicylihalamides. The formal total synthesis of the (+)-salicylihalamides, the enantiomers of the naturally occurring molecules, has been reported earlier by our group.[7e] Subsequently, we adapted the chiral pool approach strategy also toward the synthesis of the (−)-salicylihalamides.

As a potential chiral source, L-glucose, the enantiomer of the previously used D-glucose, could be easily employed following our earlier developed synthetic route. Although L-glucose is also commercially available, it is significantly more expensive than the naturally occurring D-glucose, limiting its usefulness as a starting material. Thus, we modified our hitherto developed synthesis to prepare the naturally occurring salicylihalamides, again employing D-glucose as the chiral source. In addition, we developed

SCHEME 1



a closely related chiral pool approach, using readily available L-rhamnose as the starting material.[9] The retrosynthetic approach of our synthesis of the (−)-salicylihalamides is outlined in Scheme 1.

We reasoned that the labile enamide side-chain functionality would be best installed at a very late stage of our synthetic approach leading to aldehyde **3**, which can be transformed into salicylihalamides A and B following a known procedure.[6d]

For the macrocyclic core structure **3**, we considered disconnection at the lactone functionality, at the endocyclic double bond, and at C16 resulting in fragments **4**, **5**, and **6**.

The aromatic part **4** can be obtained from commercially available *o*-anisic acid in one step,[7e] the aliphatic building block **5** is accessible from the known alcohols **7** or **8**, and the stabilized ylide **6**, needed for the two-carbon homologation, is also commercially available. Alcohol **7** can be prepared in five steps from 1,2,5,6-diacetone-D-glucose[8] and diol **8** from L-rhamnose[9] in four steps.

The first step in our synthetic approach to the (−)-salicylihalamides starting from alcohol **7** was its conversion to bromide **9** (Scheme 2).[10] Subsequent reaction with a higher order allylcuprate[11] gave rise to allylated compound **10** with overall retention of stereochemistry at C12 in the two-step process. Hydrolysis of acetonide **10** with 70% acetic acid provided lactol **11**, which was oxidized selectively to lactone **12**.

Esterification of the remaining hydroxyl function at C15 with aromatic fragment **13** using DCC as the coupling reagent gave rise to lactone **14** in excellent yield (Scheme 3). Selective reduction of **14** with DIBAL−H at −78 °C furnished the corresponding lactol anomers **15**, which, employing a Wittig reaction with stabilized ylide

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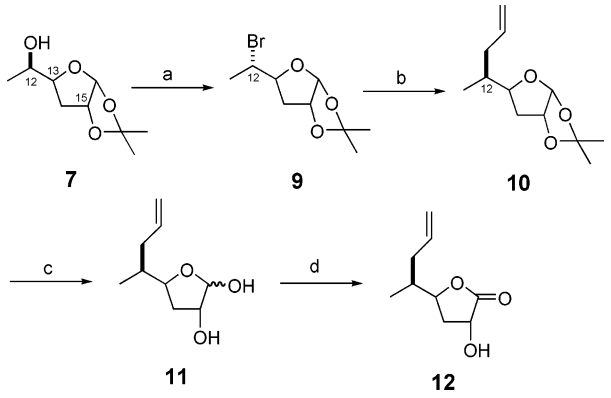
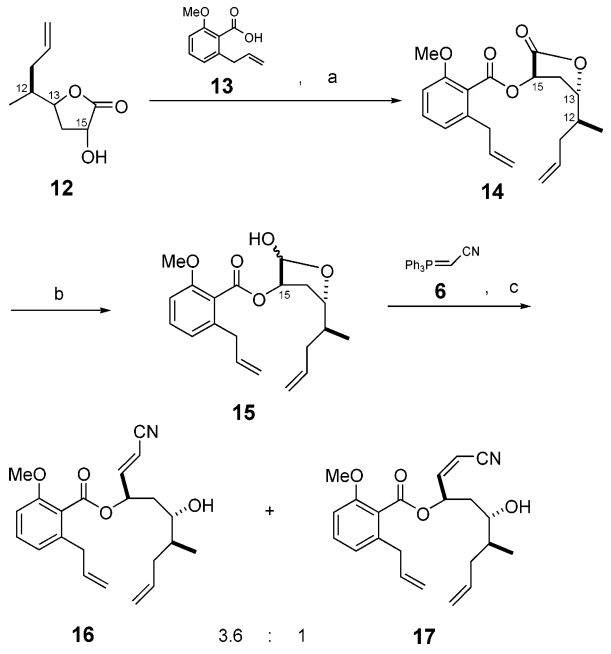
SCHEME 2[a]



[a] Reagents and conditions: (a) CBr_4, PPh_3, THF, 0 °C to rt, 6 h, 90%; (b) $(allyl)_2Cu(CN)Li_2$, THF, Et_2O, −78 °C, 30 min, 83%; (c) AcOH, water, 70 °C, 3 h, 85%; (d) Ag_2CO_3/Celite, PhH, reflux, 1 h, 81%.

SCHEME 3[a]

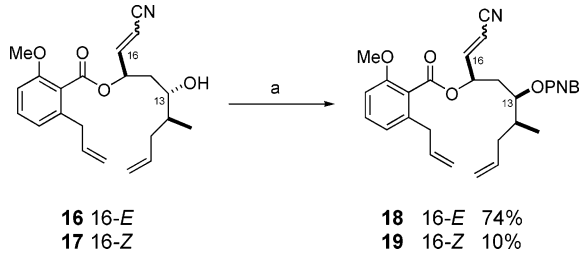


[a] Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, rt, 1 d, 95%; (b) DIBAL−H, Et_2O, −78 °C, 30 min, 93%; (c) PhMe, 80 °C, 2 h, 96%.

triphenylphosphoranylidene acetonitrile **6**, provided acryl nitriles **16** and **17** in 96% yield with an *E*:*Z* ratio of 3.6:1.

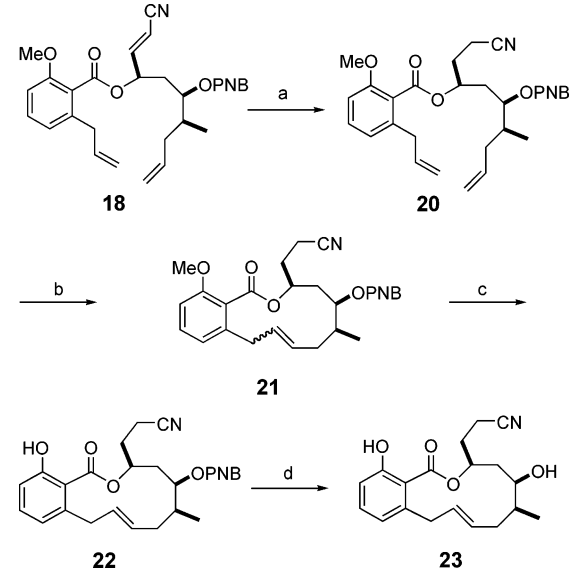
The required inversion of the chiral center at C13 in **16** and **17** was achieved by esterification under Mitsunobu conditions utilizing *p*-nitrobenzoic acid (PNBA), allowing mild cleavage of the resulting ester to the desired alcohol functionality at a later stage of the synthesis (Scheme 4).[12] Surprisingly, we noticed a considerable difference in the reactivity between **16** and **17** during the Mitsunobu esterification. Although both reactions were rather sluggish, *E*-isomer **16** gave rise to the inverted product **18** in 74% yield, whereas *Z*-isomer **17** only yielded 10% of the desired ester **19**. Apart from

SCHEME 4[a]



[a] Reagents and conditions: (a) PNBA, DEAD, PPh_3, PhMe, −30 °C to rt, 1 d.

SCHEME 5[a]



[a] Reagents and conditions: (a) $[CuHPPh_3]_6$, PhH, reflux, 45 min, 45%; (b) Grubbs I catalyst, CH_2Cl_2, reflux, 3 h, 89% (*E*:*Z* = 18:1); (c) BBr_3, CH_2Cl_2, −78 °C, 30 min, 85%; (d) K_2CO_3, MeOH, rt, 5 h, 95%.

remaining starting material, we also isolated side products in which the alcohol function had been eliminated in both cases. Presumably, the results observed above are due to steric interference of the nitrile-containing side chain, hampering the attack of the PNBA especially in *Z*-isomer **17**.

The only moderate yield (45%) of the following selective hydrogenation of *E*-acryl nitrile **18** to saturated nitrile **20** (Scheme 5)[13] might be caused by steric hindrance under these conditions because, as shown later in Scheme 8, the hydrogenation of a structurally related cyclic analogue **29** proceeded with excellent yield and enhanced reaction rate. With compound **20** in hand, we intended to close the macrocycle using ruthenium-catalyzed ring-closing metathesis.[14] Reaction of **20** with the first generation Grubbs catalyst effectively produced macrocycle **21** not only in excellent yield (89%) but also with a remark-

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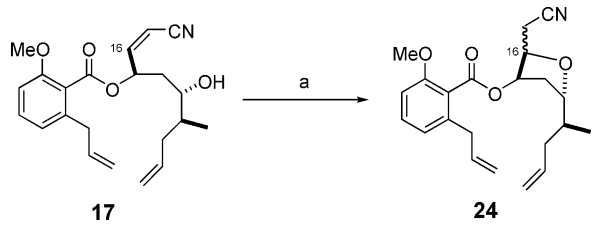
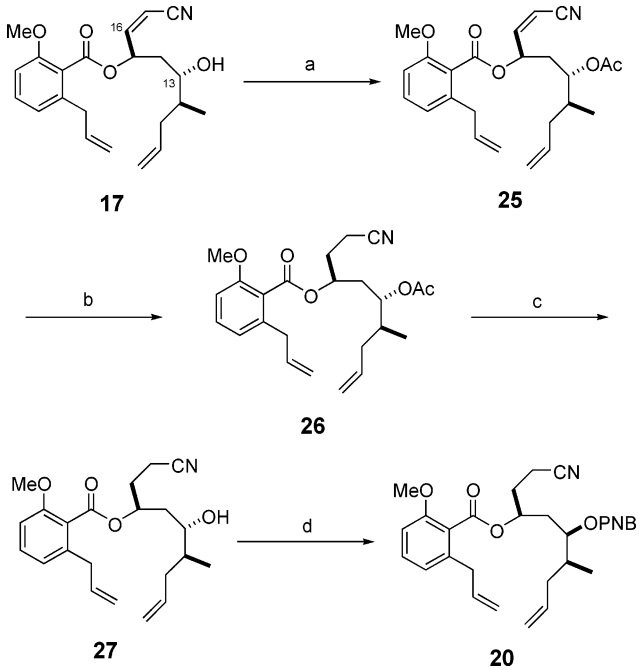
SCHEME 6[a]



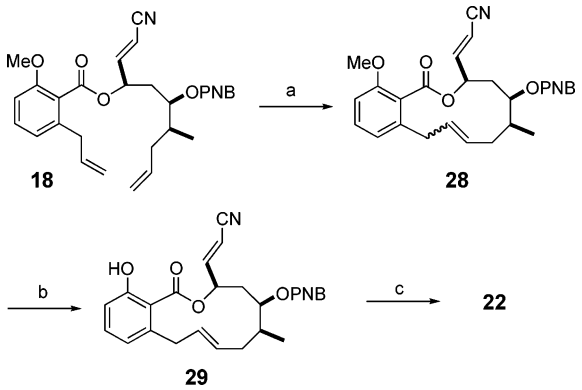
[a] Reagents and conditions: (a) $[CuHPPh_3]_6$, PhH, rt, 5 min, 67%.

SCHEME 7[a]



[a] Reagents and conditions: (a) Ac_2O, DMAP, TEA, CH_2Cl_2, rt, 3 h, 97%; (b) $[CuHPPh_3]_6$, PhH, reflux, 45 min, 87%; (c) K_2CO_3, MeOH, rt, 5 h, 89%; (d) PNBA, DEAD, PPh_3, PhMe, −30 °C to rt, 1 day, 48%.

SCHEME 8[a]



[a] Reagents and conditions: (a) Grubbs I catalyst, CH_2Cl_2, reflux, 3 h, 92% (*E*:*Z* 24:1); (b) BBr_3, CH_2Cl_2, −78 to −30 °C, 30 min, 82%; (c) $[CuHPPh_3]_6$, PhH, reflux, 2 min, 96%.

able *E*:*Z* ratio of 18:1. Cleavage of the aromatic methyl ether and separation from the undesired *Z*-isomer at this stage provided **22** in high yield (85%). Subsequent hydrolysis of the PNB group furnished the macrocyclic core structure **23**, which, in comparison with previously synthesized enantiomer *ent*-**23**,[7e] displayed identical physical properties, except for its opposite optical rotation. The conversion of *ent*-**23** to *ent*-**3** has already been published by our group, and therefore the synthesis of **23** constitutes a formal total synthesis of the (−)-salicylihalamides.[7e]

Because the Mitsunobu inversion of *Z*-acryl nitrile **17** was low-yielding (Scheme 4), we decided to explore an alternative route to convert **17** to saturated nitrile **20**. However, initial attempts to hydrogenate the *cis*-double bond of **17** with hydrido(triphenylphosphine)-copper(I) hexamer[13] only resulted in intramolecular Michael addition leading to **24**, which was isolated as a mixture of diastereoisomers (Scheme 6). To prevent the Michael addition, we protected the alcohol functionality in **17** to form acetate **25** (Scheme 7). The subsequent hydrogenation of **25** employing the above-described reaction conditions now proceeded to **26** in very good yield (87%). Cleavage of the acetate furnished alcohol **27**, which was then subjected to a Mitsunobu inversion with PNBA providing the desired intermediate **20** in 48%.

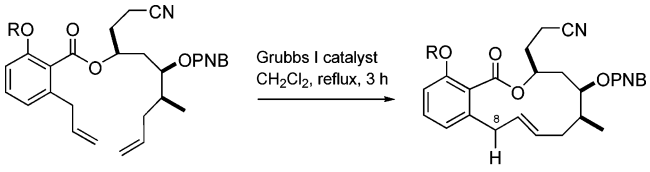
Because the hydrogenation of **18** to **20** (Scheme 5) had only proceeded in moderate yield, we decided to slightly alter our synthetic route, in an effort to optimize the overall yield of our synthetic sequence (Scheme 8). We first subjected acryl nitrile **18** to an RCM reaction, employing the first generation Grubbs catalyst, which afforded macrocycle **28** in 92% yield and an excellent 24:1 *E*:*Z* ratio. After cleavage of the phenolic methyl ether and removal of the *Z*-isomer, which led to **29** in 82% yield, reduction of the exocyclic double bond in **29** with hydrido-(triphenylphosphine)-copper(I) hexamer[13] now proceeded not only selectively but also at a significantly higher reaction rate (2 vs 45 min for the formation of **20**) furnishing **22** in high yield (96%).

Because the observed *E*:*Z* selectivity in the reaction of **20** to **21** (Scheme 5) was higher (18:1) than in any other hitherto published RCM reaction toward the synthesis of the salicylihalamides, we decided to investigate the stereochemical outcome of this particular RCM reaction in more detail.

To date, there has been no model described that can reliably predict the stereochemical outcome of RCM reactions. Thus, the optimization of the *E*:*Z* ratio concerning the salicylihalamides was achieved empirically.[6,7] In general, the presence of a protecting group at the phenol functionality was found to be crucial to obtain satisfactory amounts of the desired *E*-isomer. However, the *E*:*Z* ratio in these reactions were dependent on the substrate used in the RCM reaction.[6,7] The first generation Grubbs catalyst was shown to be more effective in producing a better *E*:*Z* ratio, as compared to the second generation catalyst.[7e]

The results of our investigations are shown in Tables 1 and 2. We first probed the influence of the phenolic protecting group on *E*:*Z* ratios (Table 1) with nitriles **20** and **30**−**32**. All substrates carried a PNB protecting group at the secondary alcohol function. The best result was achieved with a methyl substituent favoring the desired *E*-isomer with a 18:1 ratio (Table 1). Bulkier protecting groups such as TBS or TBDPS as well as the unprotected phenol resulted in inferior *E*:*Z* ratios in this special case, as compared to other substrates in which

TABLE 1. *E* and *Z* Ratios of PNB-Protected Nitriles 20 and 30−32 in RCM Reactions

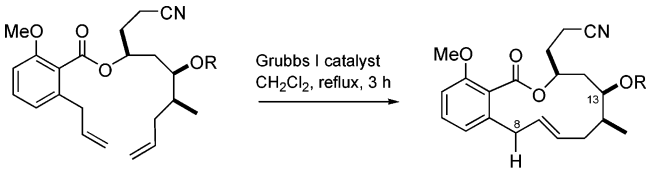


20, 30-32 **21, 38-40**

substrate[a]	R	product	yield (%)	*E*/*Z* ratio[b]
30	H	**38**	41	1:3
20	**Me**	**21**	**89**	**18:1**
31	TBS	**39**	94	7:1
32	TBDPS	**40**	75	3:1

[a] Synthesis of substrates: **30** from **20**, BBr_3 (95%); **31** from **30**, TBSCl (82%); **32** from **30**, TBDPSCl (88%). [b] Determined by integration of the ^{1}H NMR resonance of H8 and/or HPLC traces.

TABLE 2. *E* and *Z* Ratios of Me-Protected Nitriles 20 and 33−37 in RCM Reactions



20, 33-37 **21, 41-45**

substrate[a]	R	product	yield (%)	*E*/*Z* ratio[b]
33	H	**41**	44	29:1
34	Ac	**42**	87	26:1
35	MOM	**43**	84	23:1
36	Piv	**44**	94	22:1
20	PNB	**21**	89	18:1
37	TBS	**45**	94	16:1

[a] Synthesis of substrates: **33** from **20**, K_2CO_3 (94%); **34** from **33**, Ac_2O (97%); **35** from **33**, MOMCl (87%); **36** from **33**, PivCl (89%); **37** from **33**, TBSOTf (83%). [b] Determined by integration of the ^{1}H NMR resonance of H8 and/or HPLC traces.

sterically demanding silyl protecting groups provided the best *E*:*Z* ratios.[7a,e]

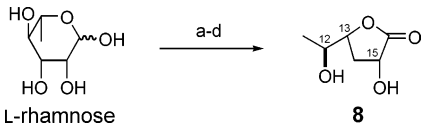
Having identified the methyl substituent as the best protecting group at the phenolic moiety to achieve an optimized *E*:*Z* ratio in our system, we investigated the influence of different protecting groups at the C13 secondary alcohol employing substrates **20** and **33**−**37** (Table 2). Overall, we found that these groups had only a minor effect on the *E*:*Z* ratios; however, all groups resulted in outstandingly high *E*:*Z* ratios (Table 2), including the reaction with the unprotected substrate **33**.

Although this synthetic route already represented a convenient and efficient formal chiral pool synthesis of the (−)-salicylihalamides (12 steps from **7** to **23**, 17% overall yield), we sought to develop an even shorter pathway starting from commercially available L-rhamnose, using building block **8** (Schemes 1 and 9), which was prepared in four steps by slight modifications of known procedures (Scheme 9).[9]

In contrast to the previously utilized alcohol **7**, rhamnose-derived diol **8** possesses the correct absolute configuration at C13 and C15, whereas an inversion at C12 is required. The synthesis started with esterification of diol **8** with the aromatic building block **13**, using EDCI as the coupling reagent, and proceeded with excellent regioselectivity (Scheme 10). Due to the lower steric restriction of the constrained endocyclic alcohol as compared to the more flexible exocyclic hydroxyl group, we were able to achieve the esterification with **13** selectively at the C15 hydroxyl group of **8** to form **46** exclusively. Reduction of the lactone moiety in **46** with DIBAL−H followed by protection of the anomeric hydroxyl groups gave rise to the methyl acetals **47** as a mixture of anomers.

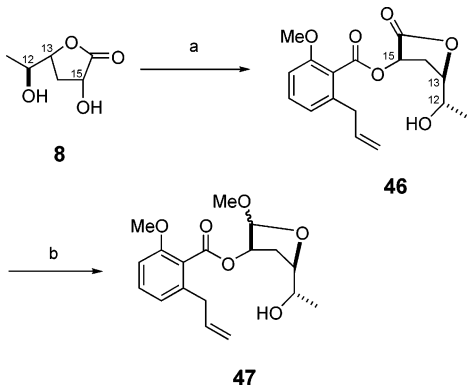
Introduction of the allyl substituent at C12 was accomplished by activating the secondary hydroxyl group as its triflate **48**, followed by reaction with a higher order allylcuprate (Scheme 11). This reaction did not proceed as smoothly as the related allylation reaction of **9** to **10** (Scheme 3). As a side reaction, even at low temperature, we observed that triflate displacement competed with

SCHEME 9[a]



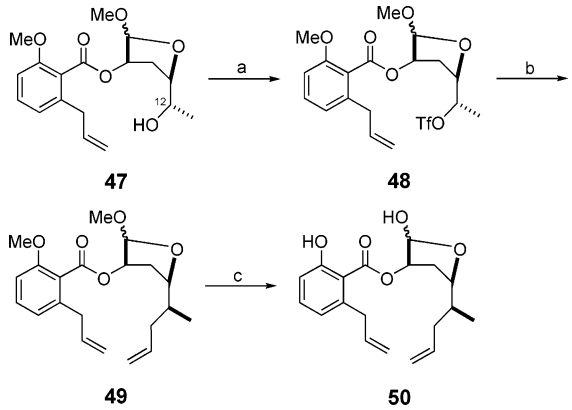
[a] Reagents and conditions: (a) $BaCO_3$, Br_2, water, rt, 1 day, 99%; (b) BzCl, pyridine, 0 °C to rt, 100%; (c) H_2 (50 psi), 10% Pd/C, TEA, EtOAc, rt, 1 day, 99%; (d) (i) NaOMe, MeOH, rt, 3 h; (ii) 1,4-dioxane, H_2SO_4, rt, 1 h, 87%.

SCHEME 10[a]



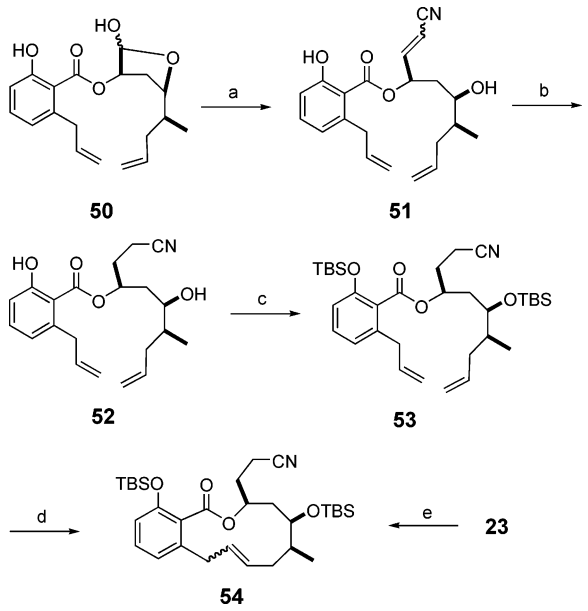
[a] Reagents and conditions: (a) **13**, EDCI, DMAP, CH_2Cl_2, rt, 14 h, 90%; (b) (i) DIBAL-H, PhMe, −78 °C, 15 min; (ii) HCl, dioxane, MeOH, rt, 8 h, 74%.

SCHEME 11[a]



[a] Reagents and conditions: (a) Tf_2O, pyridine, 0 °C, 15 min; (b) $(allyl)_2Cu(CN)Li_2$, −90 °C, 30% (two steps); (c) BCl_3, CH_2Cl_2, −78 °C, 30 min, 48−72%.

SCHEME 12[a]



[a] Reagents and conditions: (a) PPh_3=CHCN, PhMe, 80 °C, 1 h, 98% (*E*:*Z* = 23:2); (b) $[CuHPPh_3]_6$, PhH, 0 °C to rt, 15 min, 80%; (c) TBSOTf, pyridine, CH_2Cl_2, 0 °C to rt, 5 h, 91%; (d) $(PCy_3)_2Cl_2Ru$=CHPh, CH_2Cl_2, reflux, 12 h, 81% (*E* isomer) and 17% (*Z* isomer); (e) TBSOTf, pyridine, CH_2Cl_2, rt, 4 h, 97%.

ester cleavage. Nevertheless, the desired allylated product **49** was obtained in 30% yield over two steps from **47**. Cleavage of both methyl ethers in **49** provided lactol **50** in 48−72% yield as a mixture of anomers.

The remaining synthetic steps (Scheme 12) were performed in analogy to our previous synthesis from D-glucose. Wittig two carbon elongation of **50** with triphenylphosphoranylidene acetonitrile (**6**) rendered acryl nitrile **51** as a mixture of *E*:*Z* isomers. Selective hydrogenation with hydrido(triphenylphosphine)-copper-(I) hexamer[13] afforded compound **52**, which was protected with a TBS group at both hydroxyl functionalities, affording **53**. Ring-closing metathesis with the first generation Grubbs catalyst gave rise to macrocycle **54** in 98% yield (*E* and *Z* together, 81% of *E*-isomer was isolated) and a 4.7:1 *E*:*Z* ratio (separable isomers). Because this reaction yielded only slightly more of the undesired *Z*-isomer in comparison to the reaction of **20** to **21**, we refrained from exploring additional protecting groups to improve the *E*:*Z* ratio.

To verify the correct structural assignment of **54**, the hydroxyl groups in **23** (from Scheme 5) were protected as TBS ethers, also leading to core structure **54** (Scheme 12). This compound prepared via the two herein presented separate synthetic sequences exhibited identical physical properties. The synthesis of **54** constitutes a formal total synthesis of the (−)-salicylihalamides.[7e]

In summary, we have achieved two efficient formal chiral pool syntheses of the salicylihalamides A and B. In the first approach, the synthesis of macrocycle **23** from known alcohol **7** was completed in 12 steps and 17% overall yield. The second approach allowed the synthesis of **54** from known diol **8** in nine steps and 6% overall yield. In addition, we investigated the stereochemical outcome of the ring-closing metathesis with our specific, nitrile-containing substrates, using various protecting groups. In all cases, we observed high *E*:*Z* ratios. Furthermore, we demonstrated that the substituent at the phenolic functionality had a significant impact on the *E*:*Z* ratio. The methyl substituent provided the best *E*:*Z* proportion in this specific case. Protecting groups at the secondary alcohol function, however, had no significant influence on *E*:*Z* ratios.

Experimental Section

General Methods. Tetrahydrofuran was dried by distillation from sodium/benzophenone. Methylene chloride was dried by distillation from calcium hydride. All reactions involving dry solvents were carried out under an argon atmosphere. Extractive workups were carried out using the solvents mentioned in the procedures and water (three extractions). The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated under reduced pressure. Column chromatography was performed on silica gel (0.040−0.063 mm, 230−400 mesh ASTM) with the solvent systems indicated in the procedures.

7-((1*S*)-1-Bromoethyl)(1*R*,5*R*,7*S*)-3,3-dimethyl-2,4,6-trioxabicyclo[3.3.0]octane (9). Carbon tetrabromide (1.96 g, 5.91 mmol) was added in portions to an ice-cooled solution of **7** (371 mg, 1.97 mmol) and triphenylphosphine (1.65 g, 6.30 mmol) in THF (20 mL). The resulting yellow solution was stirred for 1 h at 0 °C, for an additional 6 h at rt, and then quenched with methanol (5 mL). The mixture was carefully concentrated under reduced pressure and immediately loaded onto a silica gel column. Column chromatography (EtOAc:hexanes 1:4) afforded 444 mg (90%) of bromide **9** as a colorless solid: mp 42−43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (d, 1H, J = 3.7 Hz), 4.76 (t, 1H, J = 4.3 Hz), 4.27 (dt, 1H, J = 10.4, 4.7 Hz), 4.12 (dq, 1H, J = 6.9, 5.0 Hz), 2.16 (dd, 1H, J = 13.4 Hz, 4.6 Hz), 1.77 (ddd, 1H, J = 13.4, 10.4, 4.9 Hz), 1.71 (d, 3H, J = 6.9 Hz), 1.52 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.4, 105.6, 81.2, 80.4, 49.9, 36.4, 26.8, 26.2, 22.0. The data are in accordance with reported values.[10]

7-((1*S*)-1-Methylbut-3-enyl)(1*R*,5*R*,7*S*)-3,3-dimethyl-2,4,6-trioxabicyclo[3.3.0]octane (10). To a suspension of thoroughly dried copper(I) cyanide (4.0 g, 44.7 mmol) in dry THF (30 mL) was added dropwise a solution of MeLi (59 mL, 1.5 M in Et_2O, 88.5 mmol) at −78 °C. The resulting greenish solution was gradually warmed to 0 °C followed by the addition of neat allyltributyltin (27 mL, 87 mmol). After being stirred for 30 min at 0 °C, the solution was again cooled to −78 °C. To this reaction mixture was added a solution of **9** (3.68 g, 14.7 mmol) in THF (30 mL) dropwise. The resulting mixture was stirred at −78 °C for 1 h, and then carefully quenched by the addition of a concentrated ammonium hydroxide solution, saturated with NH_4Cl, slowly warmed to rt, and stirred for an additional 3 h. Extractive workup followed by column chromatography (EtOAc:hexanes 1:9) gave 2.57 g (83%) of **10** as a colorless and volatile oil: $[\alpha]^{20}_D$ −14 (*c* 1.6 $CHCl_3$); IR (neat) 3076, 2980, 1641, 1372, 1214, 1165, 1073, 1023 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (d, 1H, J = 3.8 Hz), 5.79−5.71 (m, 1H), 5.05−4.99 (m, 2H), 4.70 (t, 1H, J = 4.3 Hz), 4.01 (ddd, 1H, J = 10.9, 6.7, 4.2 Hz), 2.19 (ddt, 1H, J = 13.7, 4.7, 1.5 Hz), 2.04 (dd, 1H, J = 13.3, 4.2 Hz), 1.85 (ddt, 1H, J = 13.8, 7.9, 0.9 Hz), 1.73−1.64 (m, 1H), 1.54 (ddd, 1H, J = 13.3, 10.9, 4.8 Hz), 1.50 (s, 3H), 1.30 (s, 3H), 0.96 (d, 3H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 116.2, 110.7, 105.1, 81.7, 80.4, 37.3, 36.6, 36.3, 26.6, 26.1, 15.9; HRMS *m*/*z* calcd for $C_{12}H_{24}NO_3$ (M + NH_4) 230.1756, found 230.1761.

5-((1*S*)-1-Methylbut-3-enyl)(3*R*,5*S*)oxolane-2,3-diol (11). A solution of **10** (2.57 g, 12.1 mmol) in 70% aqueous acetic acid was stirred at 70 °C for 3 h. The reaction mixture was concentrated in vacuo and subsequently extracted with chloroform. The organic layer was concentrated, and the residue was treated with K_2CO_3 (6.91 g, 50 mmol) in MeOH (100 mL). Evaporation of the solvent and subsequent column chromatography (EtOAc) gave rise to 1.77 g (85%) of **11** as a colorless

solid (approximately 1:1 mixture of anomers): $[\alpha]^{20}_D$ +18 (*c* 1.2, $CHCl_3$, 24 h); IR (KBr) 3377, 2929, 1703, 1641, 1035, 913 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, two anomers) δ 5.80−5.69 (m, 1H), 5.31 (s, 0.5H), 5.24 (s, 0.5H), 5.04−4.98 (m, 2H), 4.84 (s, br, 0.5H), 4.26 (s, br, 0.5H), 4.19−4.08 (m, 2H), 3.37 (d, br, 0.5H, J = 4.7 Hz), 3.31 (s, br, 0.5 H), 2.21−2.12 (m, 1H), 1.98−1.78 (m, 3H), 1.68−1.53 (m, 2H), 0.96 (d, 1.5H, J = 6.6 Hz), 0.89 (d, 1.5H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, two anomers) δ 136.6, 136.5, 116.2, 116.2, 102.2, 96.7, 83.9, 80.6, 76.4, 71.7, 38.7, 37.5, 37.3, 37.0, 35.6, 35.1, 15.9, 15.0; HRMS (EI) *m/z* calcd for $C_9H_{16}O_3Li$ (M + Li) 179.1259, found 179.1254.

5-((1*S*)-1-Methylbut-3-enyl)(3*R*,5*S*)-3-hydroxy-3,4,5-trihydrofuran-2-one (12). A suspension of **11** (1.67 g, 9.70 mmol) and silver carbonate on Celite (25 g, 50 wt %, 45 mmol) in benzene (100 mL) was refluxed for 1 h. The resulting mixture was filtered through a pad of silica gel, and the filtrate was concentrated in vacuo to give rise to 1.34 g (81%) of **12** as a pale yellow oil after column chromatography (EtOAc:hexanes 2:3): $[\alpha]^{20}_D$ +102 (*c* 0.7, $CHCl_3$); IR (neat) 3420, 2969, 2932, 1771, 1641, 1189, 1119, 995, 958, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77−5.71 (m, 1H), 5.07 (d, 1H, J = 15.7 Hz), 5.06 (d, 1H, J = 11.5 Hz), 4.55 (dt, 1H, J = 5.9, 6.9 Hz), 4.49 (t, 1H, J = 7.4 Hz), 3.42 (s, br, 1H), 2.35−2.27 (m, 2H), 2.23−2.16 (m, 1H), 1.98−1.91 (m, 1H), 1.79−1.72 (m, 1H), 0.96 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 135.4, 117.3, 82.1, 67.6, 37.6, 36.8, 33.4, 14.4; HRMS (EI) calcd for $C_9H_{15}O_3$ (M + H) 171.1021 found 171.1012.

5-((1*S*)-1-Methylbut-3-enyl)(3*R*,5*S*)-2-oxo-3-3,4,5-trihydrofuryl 6-Methoxy-2-prop-2-enylbenzoate (14). A solution of **12** (221 mg, 1.30 mmol), 2-allyl-6-methoxybenzoic acid (**13**, 319 mg, 1.66 mmol), DCC (546 mg, 2.65 mmol), and DMAP (156 mg, 1.28 mmol) in CH_2Cl_2 (2 mL) was stirred at rt for 24 h. A 1:9 mixture of EtOAc and hexanes (10 mL) was added, and the resulting suspension was stirred for 5 min and then loaded onto a silica gel column. Column chromatography (EtOAc:hexanes 1:9) afforded 425 mg (95%) of **14** as a colorless oil: $[\alpha]^{20}_D$ +40 (*c* 2.2, $CHCl_3$); IR (neat) 3078, 2968, 2933, 2841, 2359, 2342, 2255, 1790, 1739, 1640, 1585, 1518, 1471, 1438, 1268, 1194, 1109, 1068, 996, 798, 733, 648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, 1H, J = 8.0 Hz), 6.83 (d, 1H, J = 7.6 Hz), 6.79 (d, 1H, J = 8.3 Hz), 5.94−5.86 (m, 1H), 5.80−5.72 (m, 1H), 5.55 (dd, 1H, J = 8.2, 6.0 Hz), 5.10−5.04 (m, 4H), 4.61−4.56 (m, 1H), 3.81 (s, 3H), 3.50−3.35 (m, 2H), 2.51−2.41 (m, 2H), 2.26−2.20 (m, 1H), 2.02−1.95 (m, 1H), 1.84−1.78 (m, 1H), 1.00 (d, 3H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 166.8, 156.7, 139.0, 136.1, 135.2, 131.1, 121.8, 121.7, 117.3, 116.4, 109.0, 81.8, 69.0, 55.9, 37.5, 37.3, 36.6, 32.0, 14.3; HRMS (ES+) *m/z* calcd for $C_{20}H_{25}O_5$ (M + H) 345.1702, found 345.1725.

5-((1*S*)-1-Methylbut-3-enyl)(2*R*&2*S*,3*R*,5*S*)-2-hydroxyoxolan-3-yl 6-Methoxy-2-prop-2-enylbenzoate (15). To a solution of **14** (2.20 g, 6.39 mmol) in diethyl ether (30 mL) was added a solution of DIBAL−H (10 mL, 1.0 M in hexanes, 10 mmol) dropwise at −78 °C. The reaction mixture was stirred at this temperature for 30 min, quenched at −78 °C with sat. Rochelle's solution, and warmed to rt. Extractive workup with ether followed by column chromatography (EtOAc:hexanes 1:4) gave 2.07 g (93%) of **15** as a colorless oil (approximately 1:5 mixture of anomers): $[\alpha]^{20}_D$ +5.9 (*c* 1.1, $CHCl_3$, 24 h); IR (neat) 3420, 3076, 2929, 1732, 1639, 1585, 1471, 1438, 1268, 1116, 1072, 1005, 915, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, major anomer) δ 7.29 (t, 1H, J = 8.1 Hz), 6.82 (d, 1H, J = 7.6 Hz), 6.78 (d, 1H, J = 8.4 Hz), 5.95−5.85 (m, 1H), 5.80−5.72 (m, 1H), 5.46 (d, 1H, J = 3 Hz), 5.32 (s, br, 1H), 5.06−5.00 (m, 4H), 4.15−4.07 (m, 1H), 3.80 (s, 3H), 3.36 (d, 2H, J = 6.4 Hz), 3.03 (s, br, 1H), 2.24−2.08 (m, 3H), 1.90−1.82 (m, 1H), 1.72−1.63 (m, 1H), 0.99 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, major anomer) δ 167.4, 156.6, 138.4, 136.5, 136.2, 130.7, 122.3, 121.7, 116.3, 116.2, 109.0, 100.1, 84.1, 79.6, 55.8, 38.4, 37.6, 37.4, 32.6, 15.8; HRMS (ES+) calcd for $C_{20}H_{27}O_5$ (M + H) 329.1753 found 329.1739.

1-((1*E*)-2-Cyanovinyl)(1*R*,3*S*,4*S*)-3-hydroxy-4-methylhept-6-enyl 6-Methoxy-2-prop-2-enylbenzoate (16) and 1-((1*Z*)-2-Cyanovinyl)(1*R*,3*S*,4*S*)-3-hydroxy-4-methylhept-6-enyl 6-Methoxy-2-prop-2-enylbenzoate (17). A mixture of **15** (352 mg, 1.02 mmol) and (triphenylphosphoranylidene)-acetonitrile (8, 398 mg, 1.32 mmol) in toluene (10 mL) was stirred at 80 °C for 2 h. After being cooled, the mixture was directly loaded on a silica gel column. Column chromatography (EtOAc:hexanes 1:4) afforded 283 mg (75%) of the *trans*-isomer **16** (faster moving) and 77 mg (21%) of the *cis*-isomer **17** (slower moving), each of them as a pale yellow oil.

Compound **16**: $[\alpha]^{20}_D$ −25 (*c* 1.5, $CHCl_3$); IR (neat) 3520, 3074, 2970, 2929, 2841, 2227, 1732, 1639, 1585, 1471, 1439, 1269, 1109, 1070, 995, 915, 798, 757, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, 1H, J = 8.0 Hz), 6.84 (d, 1H, J = 7.7 Hz), 6.80 (d, 1H, J = 7.8 Hz), 6.76 (d, 1H, J = 4.9 Hz), 5.93−5.80 (m, 1H), 5.77−5.71 (m, 3H), 5.09−4.98 (m, 4H), 3.81 (s, 3H), 3.71 (d, 1H, J = 9.1 Hz), 3.35 (d, 2H, J = 5.3 Hz), 2.38 (s, br, 1H), 2.25−2.18 (m, 1H), 2.00−1.90 (m, 2H), 1.86−1.78 (m, 1H), 1.65−1.53 (m, 1H), 0.90 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 156.2, 151.5, 138.6, 136.8, 136.0, 130.9, 122.3, 122.0, 116.6, 116.4, 116.2, 109.0, 100.5, 72.2, 70.9, 55.7, 38.5, 38.2, 37.5, 37.1, 13.2; HRMS (FAB+) *m/z* calcd for $C_{22}H_{28}NO_4$ (M + H) 370.2018, found 370.1997.

Compound **17**: $[\alpha]_D$ −91 (*c* 1.2, $CHCl_3$); IR (neat) 3543, 3076, 2966, 2929, 2224, 1732, 1639, 1585, 1471, 1438, 1269, 1243, 1110, 1068, 995, 916, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, 1H, J = 8.0 Hz), 6.84 (d, 1H, J = 7.7 Hz), 6.80 (d, 1H, J = 8.4 Hz), 6.48 (dd, 1H, J = 11.1, 8.4 Hz), 5.95−5.74 (m, 3H), 5.50 (d, 1H, J = 11.1 Hz), 5.07−4.99 (m, 4H), 3.82 (s, 3H), 3.84−3.80 (m, 1H), 3.41 (dd, 1H, J = 15.6, 6.7 Hz), 3.32 (dd, 1H, J = 15.3, 6.3 Hz), 2.48 (s, br, 1H), 2.28−2.24 (m, 1H), 2.05−1.94 (m, 2H), 1.89−1.83 (m, 1H), 1.68−1.65 (m, 1H), 0.92 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 156.4, 151.6, 139.0, 137.1, 136.1, 131.0, 122.3, 122.1, 116.4, 116.2, 114.7, 109.1, 100.7, 73.2, 71.4, 55.9, 38.5, 38.4, 37.7, 37.3, 13.3; HRMS (FAB+) *m/z* calcd for $C_{22}H_{28}NO_4$ (M + H) 370.2018, found 370.2028.

(4*E*)-(1*R*,3*R*)-1-((1*S*)-1-Methylbut-3-enyl)-5-cyano-3-(6-methoxy-2-prop-2-enylphenylcarbonyloxy)pent-4-enyl 4-Nitrobenzoate (18). To a solution of **16** (280 mg, 0.76 mmol) and triphenylphosphine (755 mg, 2.88 mmol) in toluene (5 mL) was added *p*-nitrobenzoic acid (487 mg, 2.91 mmol). The resulting suspension was cooled to −30 °C. Diethyl azodicarboxylate (0.47 mL, 520 mg, 2.99 mmol) was added dropwise, and the reaction mixture was allowed to reach rt overnight and then stirred for an additional 24 h. The resulting solution was directly loaded on a silica gel column. Column chromatography (EtOAc:hexanes 1:9) afforded 290 mg (74%) of **18** as a pale yellow oil: $[\alpha]^{20}_D$ +32 (*c* 0.90, $CHCl_3$); IR (neat) 3075, 2972, 2226, 1726, 1640, 1585, 1527, 1471, 1348, 1274, 1103, 1069, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, 2H, J = 8.7 Hz), 8.11 (d, 2H, J = 8.8 Hz), 7.27 (t, 1H, J = 8.0 Hz), 6.81 (d, 1H, J = 7.7 Hz), 6.73 (d, 1H, J = 9.3 Hz), 6.73 (dd, 1H, J = 15.1 Hz, 5.8 Hz), 5.94−5.70 (m, 4H), 5.32−5.29 (m, 1H), 5.08−5.00 (m, 4H), 3.80 (s, 3H), 3.35 (d, 2H, J = 5.9 Hz), 2.23−1.95 (m, 5H), 0.97 (d, 3H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 163.9, 156.3, 150.7, 150.3, 138.7, 136.2, 135.6, 135.3, 130.8, 130.5, 123.4, 122.2, 121.8, 116.9, 116.5, 116.4, 108.7, 101.4, 74.4, 69.9, 55.6, 37.1, 36.8, 36.3, 34.1, 14.5; HRMS (FAB+) *m/z* calcd for $C_{29}H_{34}N_3O_7$ (M + NH_4) 536.2397, found 536.2391.

(4*Z*)-(1*R*,3*R*)-1-((1*S*)-1-Methylbut-3-enyl)-5-cyano-3-(6-methoxy-2-prop-2-enylphenylcarbonyloxy)pent-4-enyl 4-Nitrobenzoate (19). To a solution of **17** (74 mg, 0.200 mmol) and triphenylphosphine (210 mg, 0.80 mmol) in toluene (2 mL) was added *p*-nitrobenzoic acid (134 mg, 0.80 mmol). The resulting suspension was cooled to −30 °C. Diethyl azodicarboxylate (0.126 mL, 139 mg, 0.80 mmol) was added dropwise, and the reaction mixture was allowed to reach rt within 5 h and was then stirred for an additional 24 h. The resulting solution was directly loaded on a silica gel column. Column

chromatography (EtOAc:hexanes 1:9) afforded 10 mg (10%) of **18** as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23−8.18 (m, 4H), 7.26 (t, 1H, J = 8.0 Hz), 6.78 (d, 1H, J = 7.7 Hz), 6.71 (d, 1H, J = 8.3 Hz), 6.59 (dd, 1H, J = 11.2 Hz, 7.7 Hz), 5.92−5.75 (m, 3H), 5.53 (dd, 1H, J = 11.2, 1.2 Hz), 5.34−5.29 (m, 1H), 5.06−4.98 (m, 4H), 3.80 (s, 3H), 3.31 (d, 2H, J = 6.5 Hz), 2.23−2.10 (m, 5H), 0.98 (d, 3H, J = 6.7 Hz).

1-[(2*S*)-4-Cyano-2-(6-methoxy-2-prop-2-enylphenylcarbonyloxy)butyl](1*R*,2*S*)-2-methylpent-4-enyl 4-Nitrobenzoate (20 from 18). To a refluxing solution of **18** (303 mg, 0.58 mmol) in benzene (10 mL) were added water (0.3 mL, 17 mmol) and hydrido(triphenylphosphine)copper(I) hexamer (371 mg, 0.19 mmol). Refluxing was continued for 45 min. The mixture was filtered through a pad of silica gel, and the resulting solution was concentrated under reduced pressure. Column chromatography (EtOAc:hexanes 1:4) gave rise to 43 mg (14%) of starting material **18** and 137 mg (45%) of product **20** as a pale yellow oil: $[\alpha]^{20}_D$ +35 (*c* 1.3, $CHCl_3$); IR (neat) 3077, 2971, 2247, 1724, 1637, 1585, 1527, 1471, 1439, 1349, 1274, 1104, 1069, 917, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, 2H, J = 8.6 Hz), 8.16 (d, 2H, J = 8.5 Hz), 7.29 (t, 1H, J = 8.0 Hz), 6.83 (d, 1H, J = 7.7 Hz), 6.76 (d, 1H, J = 8.4 Hz), 5.99−5.89 (m, 1H), 5.81−5.71 (m, 1H), 5.34−5.26 (m, 2H), 5.09−5.00 (m, 4H), 3.82 (s, 3H), 3.38 (d, 2H, J = 6.2 Hz), 2.64−2.51 (m, 2H), 2.24−2.19 (m, 1H), 2.14−2.02 (m, 5H), 1.98−1.94 (m, 1H), 0.97 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 164.1, 156.3, 150.4, 138.5, 136.4, 135.9, 135.6, 130.7, 130.6, 123.5, 122.9, 121.9, 119.2, 116.8, 116.4, 108.8, 75.0, 69.7, 55.7, 37.1, 36.9, 36.3, 34.3, 30.6, 14.6, 13.1; HRMS (FAB+) *m/z* calcd for $C_{29}H_{36}N_3O_7$ (M + NH_4) 538.2553, found 538.2559.

(8*E*&8*Z*)-(3*S*,5*R*,6*S*)-3-(2-Cyanoethyl)-14-methoxy-6-methyl-1-oxo-2,3,4,5,6,7,10-heptahydrobenzo[*f*][12]-annulen-5-yl 4-Nitrobenzoate (21). A solution of **20** (52 mg, 100 μmol) and bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (Grubbs I catalyst, 20 mg, 24 μmol) in degassed CH_2Cl_2 (30 mL) was refluxed for 3 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc:hexanes 1:4) to give 44 mg (89%) of **21** as a pale yellow oil (inseparable 18:1 mixture of *E*/*Z*-isomers): $[\alpha]^{20}_D$ −40 (*c* 1.5, $CHCl_3$); IR (neat) 2962, 2247, 1725, 1598, 1583, 1526, 1468, 1439, 1349, 1272, 1116, 971, 756, 721 cm^{-1}. *E*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, 2H, J = 8.9 Hz), 8.22 (d, 2H, J = 8.9 Hz), 7.28 (t, 1H, J = 8.1 Hz), 6.83 (d, 1H, J = 9.1 Hz), 6.81 (d, 1H, J = 8.3 Hz), 5.73 (dd, 1H, J = 9.2, 3.2 Hz), 5.68−5.65 (m, 1H), 5.42 (ddd, 1H, J = 15.1, 9.3, 2.2 Hz), 5.21 (ddd, 1H, J = 11.0, 8.6, 3.7 Hz), 3.80 (s, 3H), 3.37 (d, 1H, J = 16.1 Hz), 2.76−2.69 (m, 1H), 2.54−2.46 (m, 1H), 2.42−2.30 (m, 3H), 2.12−1.99 (m, 3H), 1.89−1.77 (m, 2H), 0.93 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 164.0, 156.3, 150.4, 139.2, 135.9, 130.7, 130.6, 130.4, 129.2, 123.6, 123.5, 123.0, 119.2, 109.4, 77.0, 71.7, 55.6, 37.6, 37.5, 34.2, 33.4, 31.8, 13.6, 13.1; HRMS (FAB+) *m/z* calcd for $C_{27}H_{32}N_3O_7$ (M + NH_4), 510.2240 found 510.2268.

(8*E*)-(3*S*,5*R*,6*S*)-3-(2-Cyanoethyl)-14-hydroxy-6-methyl-1-oxo-2,3,4,5,6,7,10-heptahydro-benzo[*f*][12]annulen-5-yl 4-Nitrobenzoate (22). To a solution of **21** (49 mg, 99 μmol) in CH_2Cl_2 (4 mL) was added boron tribromide (0.2 mL, 1 M in CH_2Cl_2, 0.20 mmol) at −78 °C, and the resulting mixture was stirred at −78 °C for 30 min. The reaction mixture was quenched at −78 °C with sat. K_2CO_3 solution. Extractive workup with ether and column chromatography (acetone:hexanes 3:7) afforded 40 mg (85%) of product **22** as a colorless solid: mp 97−100 °C; $[\alpha]^{20}_D$ −38 (*c* 1.7, MeOH); IR (neat) 3349, 2969, 2931, 2249, 1724, 1607, 1589, 1527, 1465, 1349, 1288, 1118, 1063, 970, 721 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.28 (br s, 1H), 8.31 (d, 2H, J = 8.9 Hz), 8.28 (d, 2H, J = 8.8 Hz), 7.16 (t, 1H, J = 7.9 Hz), 6.83 (d, 1H, J = 8.1 Hz), 6.72 (d, 1H, J = 7.4 Hz), 5.64 (dd, 1H, J = 8.9, 2.4 Hz), 5.57−5.51 (m, 1H), 5.43−5.37 (m, 1H), 5.23 (dd, 1H, J = 14.4, 7.2 Hz), 3.64 (dd, 1H, J = 16.2, 8.5 Hz), 3.39 (d, 1H, J = 16.3 Hz), 2.81−2.75 (m, 1H), 2.69−2.60 (m, 1H), 2.40−2.27 (m, 2H), 2.11−1.84 (m, 5H), 0.91 (d, 3H, J = 6.5 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 168.9, 164.7, 156.2, 151.5, 140.5, 137.0, 131.6, 131.5, 130.8, 130.7, 124.4, 122.6, 122.4, 120.3, 115.2, 78.0, 72.8, 38.3, 38.2, 34.5, 34.2, 32.4, 13.9, 13.6; HRMS (FAB+) *m/z* calcd for $C_{26}H_{30}N_3O_7$ (M + NH_4) 496.2084 found 496.2109.

(8*E*)-3-((3*S*,5*R*,6*S*)-5,14-Dihydroxy-6-methyl-1-oxo-2,3,4,5,6,7,10-heptahydrobenzo[*d*][12]-annulen-3-yl)propanenitrile (23). A mixture of **22** (31 mg, 65 μmol) and potassium carbonate (72 mg, 0.52 mmol) in methanol (4 mL) was stirred at rt for 5 h. The suspension was neutralized with 2 N HCl. Extractive workup with ethyl acetate and column chromatography (acetone:hexanes 2:3) gave rise to 20 mg (95%) of the desired product **23** as a colorless solid: mp 198−200 °C (MeOH, dec); $[\alpha]^{20}_D$ −30 (*c* 1.1, MeOH); IR (KBr) 3440−3185, 2247, 2247, 1701, 1680, 1469, 1294, 1047, 778 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.21 (s, br, 1H), 7.13 (t, 1H, J = 7.8 Hz), 6.81 (d, 1H, J = 8.1 Hz), 6.68 (d, 1H, J = 7.4 Hz), 5.36−5.21 (m, 3H), 4.13−4.10 (m, 1H), 3.67−3.65 (m, 1H), 3.53 (dd, 1H, J = 16.0, 8.3 Hz), 3.31 (d, 1H, J = 16.2 Hz), 2.73−2.65 (m, 2H), 2.24−2.21 (m, 1H), 2.00−1.66 (m, 5H), 1.32−1.25 (m, 1H), 0.81 (d, 3H, J = 6.7 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 168.9, 155.9, 140.4, 131.8, 131.1, 129.6, 123.0, 122.5, 120.4, 115.0, 73.7, 70.8, 38.5, 38.3, 38.1, 37.5, 32.9, 13.6, 13.4; HRMS (FAB+) *m/z* calcd for $C_{19}H_{24}NO_4$ (M + H) 330.1705, found 330.1701.

5-((1*S*)-1-Methylbut-3-enyl)(2*R*&2*S*,3*S*,5*S*)-2-(cyanomethyl)oxolan-3-yl 2-Methoxy-6-prop-2-enylbenzoate (24). To a solution of **17** (30 mg, 0.080 mmol) in benzene (1 mL) was added hydrido(triphenylphosphine)copper(I) hexamer (130 mg, 0.067 mmol), and the mixture was stirred at rt for 30 min. The mixture was filtered through a pad of silica gel, washed several times with benzene, and the filtrate was concentrated under reduced pressure. Column chromatography (EtOAc:hexanes 1:9) gave 20 mg (67%) of **24** as a mixture of diastereomers (approximately 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, 1H, J = 8.0 Hz), 6.84 (d, 1H, J = 7.7 Hz), 6.81 (d, 1H, J = 8.4 Hz), 5.95−5.87 (m, 1H), 5.80−5.74 (m, 1H), 5.22−5.20 (m, 1H), 5.09−4.99 (m, 4H), 4.18−4.15 (m, 1H), 3.95−3.93 (m, 1H), 3.82 (s, 3H), 3.37−3.35 (d, 2H, J = 6.4 Hz), 2.85 (t, 2H, J = 4.5 Hz), 2.28−2.20 (m, 1H), 2.15 (ddd, 1H, J = 13.8 Hz, 5.1 Hz, 1.3 Hz), 2.10−2.05 (m, 1H), 1.96−1.85 (m, 1H), 1.81−1.73 (m, 1H), 1.00 (d, 3H, J = 6.7 Hz).

1-((1*S*)-1-Methylbut-3-enyl)(1*S*,3*R*)(4*Z*)-5-cyano-3-(6-methoxy-2-prop-2-enylphenylcarbonyloxy)pent-4-enyl Acetate (25). A solution of **17** (523 mg, 1.42 mmol), triethylamine (0.3 mL, 218 mg, 2.15 mmol), acetic anhydride (0.2 mL, 216 mg, 2.12 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (5 mL) was stirred at rt for 3 h. The reaction mixture was quenched by addition of methanol (1 mL). Evaporation under reduced pressure and column chromatography (EtOAc:hexanes 1:4) gave 565 mg (97%) of **25** as colorless oil: $[\alpha]^{20}_D$ −49 (*c* 0.90, $CHCl_3$); IR (neat) 3076, 2973, 2936, 2842, 2360, 2342, 2223, 1732, 1640, 1585, 1471, 1438, 1372, 1268, 1238, 1107, 1067, 916, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, 1H, J = 8.0 Hz), 6.81 (d, 1H, J = 8.4 Hz), 6.79 (d, 1H, J = 8.4 Hz), 6.43 (dd, 1H, J = 11.1, 8.5 Hz), 5.83−5.93 (m, 2H), 5.78−5.69 (m, 1H), 5.54 (d, 1H, J = 11.2 Hz), 5.07−4.94 (m, 5H), 3.82 (s, 3H), 3.35 (d, 2H, J = 6.5 Hz), 2.28−2.20 (m, 2H), 2.07 (s, 3H), 2.02−1.97 (m, 1H), 1.91−1.84 (m, 2H), 0.94 (d, 3H, J = 6.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 166.8, 156.6, 150.3, 138.6, 136.3, 136.1, 130.8, 122.5, 121.7, 116.5, 114.5, 109.0, 102.2, 77.2, 72.6, 70.6, 55.8, 37.4, 37.0, 35.9, 34.6, 21.2, 14.0; HRMS (FAB+) *m/z* calcd for $C_{24}H_{30}NO_5$ (M + H) 412.2124, found 412.2103.

1-[(2*S*)-4-Cyano-2-(6-methoxy-2-prop-2-enylphenylcarbonyloxy)butyl](1*S*,2*S*)-2-methylpent-4-enyl Acetate (26). To a refluxing solution of **25** (555 mg, 1.35 mmol) in benzene (15 mL) containing a drop of water was added hydrido(triphenylphosphine)copper(I) hexamer (1.5 g, 0.76 mmol), and the solution was refluxed for an additional 45 min. The mixture was filtered through a pad of silica gel, and the

resulting solution was concentrated under reduced pressure. Column chromatography (EtOAc:hexanes 3:7) afforded 488 mg (87%) of **26** as a colorless oil: $[\alpha]^{20}_D$ −19 (*c* 1.3, $CHCl_3$); IR (neat) 3077, 2972, 2936, 2841, 2247, 1731, 1640, 1585, 1471, 1439, 1371, 1264, 1241, 1113, 916, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, 1H, J = 8.0 Hz), 6.84 (d, 1H, J = 7.6 Hz), 6.80 (d, 1H, J = 8.3 Hz), 5.97−5.89 (m, 1H), 5.80−5.69 (m, 1H), 5.16−4.99 (m, 6H), 3.82 (s, 3H), 3.37 (d, 2H, J = 6.4 Hz), 2.60−2.42 (m, 2H), 2.20−2.11 (m, 3H), 2.09 (s, 3H), 1.95−1.75 (m, 4H), 0.93 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.4, 156.3, 138.3, 136.1, 136.1, 130.6, 123.0, 121.8, 119.1, 116.6, 116.5, 108.8, 72.6, 70.5, 55.7, 37.4, 37.2, 36.3, 35.7, 29.5, 21.0, 13.9, 13.1; HRMS (FAB+) *m/z* calcd for $C_{24}H_{32}NO_5$ (M + H) 414.2280, found 414.2287.

(1*S*,3*S*,4*S*)-1-(2-Cyanoethyl)-3-hydroxy-4-methylhept-6-enyl 6-Methoxy-2-prop-2-enylbenzoate (27). A mixture of **26** (480 mg, 1.61 mmol) and potassium carbonate (321 mg, 2.32 mmol) in methanol (10 mL) was stirred at rt for 5 h. The suspension was neutralized with acetic acid (0.22 mL) and concentrated under reduced pressure. Column chromatography (EtOAc:hexanes 3:7) yielded 385 mg (89%) of the desired alcohol **27** as a colorless oil: $[\alpha]^{20}_D$ −21 (*c* 1.2, $CHCl_3$); IR (neat) 3508, 3076, 2967, 2841, 2248, 1731, 1640, 1585, 1480, 1439, 1277, 1115, 1070, 995, 915, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, 1H, J = 8.0 Hz), 6.85 (d, 1H, J = 7.7 Hz), 6.80 (d, 1H, J = 8.3 Hz), 5.95−5.88 (m, 1H), 5.85−5.76 (m, 1H), 5.33−5.29 (m, 1H), 5.09−5.00 (m, 4H), 3.83 (s, 3H), 3.76−3.73 (m, 1H), 3.37 (d, 2H, J = 6.2 Hz), 2.60−2.41 (m, 2H), 2.24−1.90 (m, 6H), 1.77−1.72 (m, 1H), 1.68−1.59 (m, 1H), 0.91 (d, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 156.2, 138.5, 137.0, 136.2, 130.7, 123.0, 122.1, 119.3, 116.5, 116.3, 109.0, 72.6, 71.5, 55.8, 38.5, 38.3, 37.8, 37.2, 30.1, 13.3, 13.1; HRMS (FAB+) *m/z* calcd for $C_{22}H_{30}NO_4$ (M + H) 372.2175, found 372.2185.

1-[(2*S*)-4-Cyano-2-(6-methoxy-2-prop-2-enylphenylcarbonyloxy)butyl](1*R*,2*S*)-2-methylpent-4-enyl 4-Nitrobenzoate (20 from 27). To a solution of **27** (351 mg, 1.01 mmol) and triphenylphosphine (1.06 mg, 4.04 mmol) in toluene (40 mL) was added *p*-nitrobenzoic acid (675 mg, 4.04 mmol), and the suspension was cooled to −30 °C. Diethyl azodicarboxylate (0.65 mL, 719 mg, 4.13 mmol) was added dropwise, and the mixture was allowed to reach rt overnight and then stirred for an additional 24 h. The resulting solution was directly loaded on a silica gel column. Column chromatography (EtOAc:hexanes 1:4) afforded 238 mg (48%) of **20** as pale yellow oil. For data, see above.

(2*E*,8*E*&8*Z*)-3-((3*R*,5*R*,6*S*)-5-Hydroxy-14-methoxy-6-methyl-1-oxo(2,3,4,5,6,7,10-heptahydro-benzo[*d*][12]-annulen-3-yl))prop-2-enenitrile (28). A solution of **18** (390 mg, 0.75 mmol) and bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (Grubbs I catalyst, 130 mg, 0.16 mmol) in degassed CH_2Cl_2 (100 mL) was heated at reflux temperature for 3 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc:hexanes 15:85) to give 339 mg (92%) of **28** as a pale yellow oil as an inseparable 96:4 mixture of *E*/*Z*-isomers: $[\alpha]^{20}_D$ −1.5 (*c* 1.0, $CHCl_3$); IR (neat) 2962, 2928, 2226, 1725, 1527, 1275, 1114, 1074, 758, 720 cm^{-1}. *E*-**28**: ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, 2H, J = 8.7 Hz), 8.20 (d, 2H, J = 8.6 Hz), 7.31 (t, 1H, J = 8.0 Hz), 6.86 (d, 1H, J = 8.5 Hz), 6.81 (d, 1H, J = 7.6 Hz), 6.71 (dd, 1H, J = 16.2 Hz, 2.8 Hz), 5.92−5.88 (m, 2H), 5.71−5.63 (m, 2H), 5.40 (dd, 1H, J = 15.2, 9.7 Hz), 3.84−3.78 (m, 1H), 3.79 (s, 3H), 3.35 (d, 1H, J = 16.1 Hz), 2.42−2.32 (m, 2H), 2.04−1.94 (m, 2H), 1.81 (dt, 1H, J = 14.1 Hz, 11.0 Hz), 0.96 (d, 3H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 164.0, 156.5, 151.6, 150.5, 139.5, 135.7, 130.8, 130.7, 130.5, 129.6, 123.6, 123.2, 122.9, 116.8, 109.4, 100.2, 76.8, 70.6, 55.6, 37.4, 37.3, 34.1, 33.8, 14.1; HRMS (FAB+) *m/z* calcd for $C_{27}H_{27}N_2O_7$ (M + H) 491.1818, found 491.1798.

(2*E*,8*E*)-3-((3*R*,5*R*,6*S*)-5,14-Dihydroxy-6-methyl-1-oxo-(2,3,4,5,6,7,10-heptahydro-benzo[*d*][12]annulen-3-yl))-prop-2-enenitrile (29). A solution of **28** (48 mg, 98 μmol) in CH_2Cl_2 (6 mL) was charged at −78 °C with boron tribromide (0.3 mL, 1 M in CH_2Cl_2, 0.30 mmol). The resulting mixture was allowed to reach −30 °C and was stirred at this temperature for 30 min. The yellow mixture was recooled to −78 °C and quenched with 0.3 M Na_2HPO_4 solution (30 mL). Extractive workup with ethyl acetate followed by column chromatography (acetone:hexanes 3:7) afforded 38 mg (82%) of product **29** as a colorless solid: mp 100−103 °C; $[\alpha]^{20}_D$ +8.9 (*c* 1.1, MeOH); IR (neat) 3339, 2969, 2929, 2227, 1724, 1527, 1349, 1281, 1105, 720 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 9.32 (s, 1H), 8.26−8.30 (m, 4H), 7.21 (t, 1H, J = 7.9 Hz), 6.96 (dd, 1H, J = 16.1, 3.3 Hz), 6.86 (d, 1H, J = 8.2 Hz), 6.76 (d, 1H, J = 7.5 Hz), 6.07 (dd, 1H, J = 16.2, 2.2 Hz), 5.90 (d, 1H, J = 8.2 Hz), 5.61−5.52 (m, 2H), 5.38 (dd, 1H, J = 14.9, 8.2 Hz), 3.65 (dd, 1H, J = 16.0 Hz, J = 8.6 Hz), 3.38 (dd, 1H, J = 16.0, J = 2.4 Hz), 2.40−2.24 (m, 2H), 2.20 (dd, 1H, J = 15.8, 8.9 Hz), 2.02−1.99 (m, 1H), 1.90 (dt, 1H, J = 13.4, 10.4 Hz), 0.95 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 168.2, 164.8, 156.4, 153.4, 151.5, 140.8, 136.9, 131.9, 131.7, 131.0, 130.8, 124.4, 122.6, 121.9, 117.7, 115.4, 100.5, 77.6, 71.9, 38.1, 38.0, 34.6, 34.4, 14.5; HRMS (FAB+) *m/z* calcd for $C_{26}H_{28}N_3O_7$ (M + NH_4) 494.1927, found 494.1916.

(8*E*)-(3*S*,5*R*,6*S*)-3-(2-Cyanoethyl)-14-hydroxy-6-methyl-1-oxo-2,3,4,5,6,7,10-heptahydrobenzo[*f*][12]annulen-5-yl 4-Nitrobenzoate (22 from 29). To a refluxing solution of **29** (23 mg, 48 μmol) in benzene (2 mL) containing a drop of water was added hydrido(triphenylphosphine)copper(I) hexamer (80 mg, 41 μmol). Heating was continued for 2 min. The mixture was filtered through a pad of silica gel, washed with benzene, the filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (acetone:hexanes 3:7) to yield 22 mg (96%) of **22** as a colorless solid. For data, refer to the previous synthesis of **22** above.

(1*S*,3*R*,4*S*)-1-(2-Cyanoethyl)-4-methyl-3-(4-nitrophenylcarbonyloxy)hept-6-enyl 6-Hydroxy-2-prop-2-enylbenzoate (30). Boron tribromide (1 M in CH_2Cl_2, 0.37 mL, 0.37 mmol) was added dropwise at −78 °C to a solution of **20** (38 mg, 75 μmol) in CH_2Cl_2. After being stirred for 30 min, the reaction was quenched by addition of a sat. solution of K_2CO_3 at −78 °C. Extractive workup with ether followed by column chromatography (EtOAc:hexanes 3:7) afforded 35 mg (95%) of **30** as a colorless oil: $[\alpha]^{20}_D$ +62 (*c* 1.5, $CHCl_3$); IR (neat) 3078, 2975, 2933, 2361, 2248, 1724, 1658, 1607, 1527, 1450, 1348, 1273, 1119, 1103, 917, 760, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.92 (s, 1H), 8.22 (d, 2H, J = 8.9 Hz), 8.10 (d, 2H, J = 8.9 Hz), 7.29 (t, 1H, J = 7.9 Hz), 6.84 (d, 1H, J = 7.3 Hz), 6.65 (d, 1H, J = 7.5 Hz), 6.02−5.92 (m, 1H), 5.80−5.71 (m, 1H), 5.46−5.40 (m, 1H), 5.22 (dd, 1H, J = 12.4, 5.5 Hz), 5.07−5.03 (m, 2H), 5.00 (m, 1H), 5.87 (ddd, 1H, J = 17.1, 3.3, 1.6 Hz), 3.71 (dd, 1H, J = 16.1, 5.7 Hz), 3.50 (dd, 1H, J = 16.1, 5.5 Hz), 2.45−2.41 (m, 2H), 2.25−1.95 (m, 7H), 0.99 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 164.0, 163.0, 150.5, 141.8, 137.4, 135.6, 135.1, 134.7, 130.5, 123.5, 122.7, 118.5, 117.0, 116.5, 115.7, 111.5, 74.5, 70.4, 40.0, 37.0, 36.2, 34.3, 30.6, 14.8, 13.9; HRMS (FAB+) *m/z* calcd for $C_{28}H_{31}N_2O_7$ (M + H) 507.2131, found 507.2119.

1-{(2*S*)-4-Cyano-2-[2-prop-2-enyl-6-(1,1,2,2-tetramethyl-1-silapropoxy)phenylcarbonyl-oxy]butyl}(1*R*,2*S*)-2-methylpent-4-enyl 4-Nitrobenzoate (31). A solution of **30** (37 mg, 73 μmol), TBSCl (42 mg, 0.28 mmol), and imidazole (60 mg, 0.88 mmol) in DMF (1 mL) was stirred at 50 °C for 3 h. Extractive workup with ether and subsequent column chromatography (EtOAc:hexanes 1:9) gave 37 mg (82%) of silyl ether **31** as a colorless oil: $[\alpha]^{20}_D$ +17 (*c* 1.4, $CHCl_3$); IR (neat) 3078, 2959, 2931, 2858, 2248, 1728, 1640, 1608, 1582, 1594, 1529, 1464, 1348, 1275, 1103, 1025, 916, 838, 784, 739, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, 2H, J = 8.9 Hz), 8.12 (d, 2H, J = 8.9 Hz), 7.14 (t, 1H, J = 8.0 Hz), 6.75 (d, 1H, J = 7.6 Hz), 6.66 (d, 1H, J = 8.1 Hz), 5.95−5.85 (m, 1H), 5.80−5.70 (m, 1H), 5.30−5.25 (m, 1H), 5.21−5.15 (m, 1H), 5.09−5.00 (m, 4H), 3.32 (d, 2H, J = 6.3 Hz), 2.54−2.45 (m, 2H),

2.29−2.19 (m, 1H), 2.14−1.97 (m, 6H), 0.98 (d, 3H, J = 6.5 Hz), 0.95 (s, 9H), 0.22 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 164.1, 152.5, 150.4, 138.2, 136.2, 135.8, 135.4, 130.6, 130.1, 125.7, 123.5, 122.0, 118.8, 117.0, 116.9, 116.6, 75.1, 70.7, 37.4, 36.7, 36.5, 34.2, 29.9, 25.8, 18.4, 14.9, 13.7, −4.0, −4.2; HRMS (FAB+) *m/z* calcd for $C_{34}H_{45}N_2O_7Si$ (M + H) 621.2996, found 621.3008.

1-{(2*S*)-2-[6-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)-2-prop-2-enylphenylcarbonyloxy]-4-cyanobutyl}(1*R*,2*S*)-2-methylpent-4-enyl 4-Nitrobenzoate (32). A solution of **30** (7 mg, 14 μmol), TBDPSCl (0.1 mL, 106 mg, 0.39 mmol), and imidazole (50 mg, 0.73 mmol) in DMF (1 mL) was stirred at 80 °C for 6 h. Extractive workup with ether followed by column chromatography (EtOAc:hexanes 1:9) gave rise to 9 mg (88%) of silyl ether **32** as a colorless oil: $[\alpha]^{20}_D$ –8.9 (*c* 0.40, $CHCl_3$); IR (neat) 3074, 2932, 2858, 1725, 1528, 1463, 1276, 1114, 824, 719, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, 2H, J = 9.1 Hz), 8.11 (d, 2H, J = 9.1 Hz), 7.74−7.69 (m, 4H), 7.44−7.35 (m, 6H), 6.83 (t, 1H, J = 8.0 Hz), 6.62 (d, 1H, J = 7.7 Hz), 6.31 (d, 1H, J = 8.2 Hz), 5.94−5.84 (m, 1H), 5.83−5.78 (m, 1H), 5.33 (dt, 1H, J = 9.5, 4.4 Hz), 5.24−5.18 (q, 1H, J = 5.8 Hz), 5.10−5.00 (m, 4H), 3.38−3.26 (m, 2H), 2.53−2.43 (m, 2H), 2.29−1.94 (m, 7H), 1.04 (s, 9H), 0.99 (d, 3H, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 164.2, 152.3, 150.4, 138.1, 136.0, 135.9, 135.4, 135.3, 132.2, 132.0, 130.6, 130.2, 129.9, 127.9, 125.0, 123.5, 121.8, 118.8, 117.2, 117.0, 116.7, 77.2, 75.3, 71.3, 37.5, 36.7, 36.5, 34.1, 29.7, 26.5, 19.4, 15.0, 13.6; HRMS (FAB+) *m/z* calcd for $C_{44}H_{52}N_3O_7Si$ (M + NH_4) 762.3575, found 762.361.

(1*S*,3*R*,4*S*)-1-(2-Cyanoethyl)-3-hydroxy-4-methylhept-6-enyl 6-Methoxy-2-prop-2-enyl-benzoate (33). To a solution of **20** (26 mg, 53 μmol) in MeOH (2 mL) was added K_2CO_3 (100 mg, 0.72 mmol), and the mixture was stirred at rt for 3 h. Extractive workup with ether followed by column chromatography (EtOAc:hexanes 3:7) resulted in 17 mg (94%) of **33** as a colorless oil: $[\alpha]^{20}_D$ +19 (*c* 1.7, $CHCl_3$); IR (neat) 3520, 3076, 2966, 2930, 2248, 1724, 1639, 1585, 1471, 1439, 1267, 1116, 1070, 915, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, 1H, J = 8.0 Hz), 6.85 (d, 1H, J = 7.7 Hz), 6.82 (d, 1H, J = 8.3 Hz), 5.96−5.78 (m, 1H), 5.83−5.73 (m, 1H), 5.44−5.38 (m, 1H), 5.09−4.99 (m, 4H), 3.83 (s, 3H), 3.60−3.56 (m, 1H), 3.37 (d, 2H, J = 6.0 Hz), 2.75 (s, br, 1H), 2.63−2.42 (m, 2H), 2.35−2.28 (m, 1H), 2.10−2.03 (m, 2H), 1.96 (dt, 1H, J = 13.8, 7.9 Hz), 1.83−1.76 (m, 1H), 1.70−1.60 (m, 2H), 0.89 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 156.1, 138.2, 137.0, 136.1, 130.8, 122.9, 122.1, 119.2, 116.6, 116.2, 108.9, 71.3, 70.5, 55.7, 38.7, 38.6, 37.2, 37.0, 30.9, 15.3, 13.3; HRMS (FAB+) *m/z* calcd for $C_{22}H_{30}NO_4$ (M + H) 372.2175, found 372.2188.

1-[(2*S*)-4-Cyano-2-(6-methoxy-2-prop-2-enylphenylcarbonyloxy)butyl](1*R*,2*S*)-2-methyl-pent-4-enyl Acetate (34). A solution of **33** (8.5 mg, 23 μmol), triethylamine (20 μL, 14.5 mg, 0.14 mmol), acetic anhydride (14 μL, 15.1 mg, 0.15 mmol), and a catalytic amount of 4-(dimethylamino)pyridine in CH_2Cl_2 was stirred at rt for 12 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc:hexanes 3:7) to give 9.2 mg (97%) of acetyl ester **34** as colorless oil: $[\alpha]^{20}_D$ +21 (*c* 0.40, $CHCl_3$); IR (neat) 3076, 2970, 2932, 2247, 1731, 1585, 1470, 1267, 1243, 1111, 1068, 915, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, 1H, J = 8.0 Hz), 6.85 (d, 1H, J = 7.8 Hz), 6.79 (d, 1H, J = 8.3 Hz), 6.03−5.93 (m, 1H), 5.78−5.66 (m, 1H), 5.26−5.22 (m, 1H), 5.09−4.92 (m, 5H), 3.84 (s, 3H), 3.39 (d, 2H, J = 6.3 Hz), 2.66−2.46 (m, 2H), 2.16−2.08 (m, 2H), 2.05 (s, 3H), 1.92−1.76 (m, 5H), 0.87 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 167.6, 156.3, 138.6, 136.5, 136.3, 130.7, 123.2, 122.0, 119.4, 116.5, 116.4, 108.8, 73.2, 69.9, 55.8, 37.1, 37.0, 36.1, 34.1, 30.9, 21.1, 14.4, 13.0; HRMS (FAB+) *m/z* calcd for $C_{24}H_{35}N_2O_5$ (M + NH_4) 431.2546, found 431.2539.

(1*S*,3*R*,4*S*)-1-(2-Cyanoethyl)-3-(methoxymethoxy)-4-methylhept-6-enyl 6-Methoxy-2-prop-2-enylbenzoate (35). A solution of **33** (8.5 mg, 23 μmol) and chloromethyl methyl ether (0.1 mL, 106 mg, 1.32 mmol) in diisopropylethylamine (2 mL) was stirred at rt for 1 day. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc:hexanes 1:4) to afford 8.3 mg (87%) of **35** as a colorless oil: $[\alpha]^{20}_D$ +23 (*c* 0.40, $CHCl_3$); IR (neat) 3076, 2931, 2360, 2341, 1728, 1585, 1471, 1267, 1112, 1036, 916, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, 1H, J = 8.0 Hz), 6.85 (d, 1H, J = 7.7 Hz,), 6.80 (d, 1H, J = 8.3 Hz), 6.00−5.88 (m, 1H), 5.79−5.68 (m, 1H), 5.39−5.33 (m, 1H), 5.08 (dd, 1H, J = 10.1, 1.4 Hz), 5.03 (dd, 1H, J = 17.1, 1.6 Hz), 4.97 (dd, 1H, J = 18.6, 1.4 Hz), 4.94 (d, 1H, J = 9.5 Hz), 4.72 (d, 1H, J = 6.9 Hz), 4.68 (d, J = 6.9 Hz, 1H), 3.84 (s, 3H), 3.66 (ddd, 1H, J = 10.1, 3.7, 1.8 Hz), 3.41 (s, 3H), 3.37 (dd, 2H, J = 6.1 Hz, 1.1 Hz), 2.62−2.44 (m, 2H), 2.22−2.12 (m, 1H), 2.09−1.91 (m, 3H), 1.84 (dt, 1H, J = 13.1, 7.9 Hz), 1.76 (ddd, 1H, J = 14.5, 9.3, 1.8 Hz), 1.62 (ddd, 1H, J = 14.5, 10.2, 3.0 Hz), 0.90 (d, 3H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 156.2, 138.2, 136.8, 136.3, 130.6, 123.4, 121.9, 119.5, 116.6, 116.1, 108.8, 96.7, 78.0, 70.9, 56.0, 55.7, 37.6, 37.2, 36.2, 34.4, 31.2, 13.5, 13.1; HRMS (FAB+) *m/z* calcd for $C_{24}H_{37}N_2O_5$ (M + NH_4) 433.2702, found 433.2726.

1-[(2*S*)-4-Cyano-2-(6-methoxy-2-prop-2-enylphenylcarbonyloxy)butyl](1*R*,2*S*)-2-methyl-pent-4-enyl 2,2-Dimethylpropanoate (36). A solution of **33** (3.5 mg, 9.4 μmol), pivaloyl chloride (0.15 mL, 146 mg, 1.21 mmol), triethylamine (0.17 mL, 123 mg, 1.22 mmol), and 4-(dimethylamino)pyridine (5 mg, 41 μmol) in CH_2Cl_2 (0.5 mL) was heated at reflux temperature for 1 day. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc:hexanes 1:4) to afford 3.8 mg (89%) of pivaloate **36**: $[\alpha]^{20}_D$ +23 (*c* 0.20, $CHCl_3$); IR (neat) 3077, 2971, 2931, 2248, 1727, 1585, 1471, 1268, 1160, 1110, 1068, 914 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, 1H, J = 8.0 Hz), 6.85 (d, 1H, J = 7.7 Hz), 6.79 (d, 1H, J = 8.4 Hz), 6.01−5.92 (m, 1H), 5.77−5.70 (m, 1H), 5.24−5.18 (m, 1H), 5.09−4.97 (m, 4H), 4.95−4.91 (m, 1H), 3.84 (s, 3H), 3.38 (d, 2H, J = 6.2 Hz), 2.65−2.44 (m, 2H), 2.20−2.08 (m, 2H), 2.08−1.98 (m, 1H), 1.93−1.75 (m, 4H), 1.23 (s, 9H), 0.87 (d, 3H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 167.5, 156.3, 138.6, 136.5, 136.3, 130.6, 123.2, 122.0, 119.3, 116.5, 116.3, 108.8, 72.8, 69.8, 55.7, 38.9, 37.1, 36.9, 35.9, 33.9, 30.9, 27.2, 14.2, 13.1; HRMS (FAB+) *m/z* calcd for $C_{27}H_{38}NO_5$ (M + H) 456.2750, found 456.2750.

(1*S*,3*R*,4*S*)-1-(2-Cyanoethyl)-4-methyl-3-(1,1,2,2-tetramethyl-1-silapropoxy)hept-6-enyl 6-Methoxy-2-prop-2-enylbenzoate (37). To a solution of **33** (3.5 mg, 9.4 μmol) and 2,6-lutidine (50 μL, 0.43 mmol) in CH_2Cl_2 (0.5 mL) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.1 mL, 115 mg, 0.44 mmol), and the mixture was stirred at rt for 1 day. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc:hexanes 1:9) to give 3.8 mg (83%) of silyl ether **37**: $[\alpha]^{20}_D$ −13 (*c* 0.20, $CHCl_3$); IR (neat) 3077, 2929, 2856, 2248, 1731, 1585, 1471, 1263, 1111, 1068, 837, 776, 668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, 1H, J = 8.0 Hz), 6.84 (d, 1H, J = 7.7 Hz), 6.80 (d, 1H, J = 8.3 Hz), 5.93 (ddt, 1H, 16.9, 10.2, 6.4 Hz), 5.74 (ddt, 1H, J = 17.1, 10.1, 3.9 Hz), 5.25 (tt, 1H, J = 7.7, 3.9 Hz), 5.10−4.93 (m, 4H), 3.84−3.81 (m, 1H), 3.83 (s, 3H), 3.36 (d, 2H, J = 6.3 Hz), 2.59−2.45 (m, 2H), 2.20−2.15 (m, 1H), 2.07−1.97 (m, 2H), 1.87−1.67 (m, 3H), 1.58−1.51 (m, 1H), 0.91 (s, 9H), 0.87 (d, 3H, J = 6.7 Hz), 0.13 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 156.3, 138.2, 137.0, 136.2, 130.6, 123.5, 121.8, 119.4, 116.6, 116.0, 108.9, 72.2, 71.8, 55.7, 39.1, 37.5, 37.3, 36.3, 31.3, 25.9, 18.1, 13.4, 13.0, −4.2, −4.5; HRMS (FAB+) *m/z* calcd for $C_{28}H_{47}N_2O_4Si$ (M + NH_4) 503.3305, found 503.3295.

General Procedure for the RCM Reactions of Substrates 20, 30−37 To Determine the *E*:*Z* Ratios in Product Mixtures 21, 38−45. A solution of the RCM substrate (**20**, **30**−**37**) (10 μmol) and bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (Grubbs I catalyst, 2 mg, 2

μmol) in degassed CH_2Cl_2 (2 mL) was refluxed for 3 h. The solution was filtered through a pad of silca gel, and the filtrate containing the product mixtures **21**, **38**−**45** was concentrated under reduced pressure. *E*/*Z* ratios were determined by ^{1}H NMR spectroscopy and HPLC analysis (see Supporting Information). For NMR analysis, the integral of the characteristic doublet of one of the H8 protons appearing at around δ 3.4 ppm, which belongs to the *E*-isomer, was compared to the corresponding H8 proton of the *Z*-isomer, which typically appears at δ 3.1 ppm. HPLC analysis was carried out on a silica gel column with a gradient of ethyl acetate and hexanes. Peaks were detected at 280 nm. Specific information for each example is provided with the ^{1}H NMR spectra in the Supporting Information.

(3*R*,5*R*,6*S*)-3-Hydroxy-5-(hydroxyethyl)-3,4,5-trihydrofuran-2-one (8).[9] To a suspension of L-rhamnose (25 g, 0.14 mol) and $BaCO_3$ (35 g, 0.18 mol) in water (250 mL) in a round-bottom flask, wrapped with aluminum foil, was carefully added Br_2 (7.7 mL, 0.15 mol) by syringe over 30 min. The brown suspension was stirred overnight, turning into a yellow solution the following day. Additional Br_2 (0.3 mL, 5.8 mmol) was added to force the reaction to completion. After 1 h, the solution was acidified with concentrated HCl to pH 3. The reaction mixture was then filtered through a fine glass filter, and the filtrate was evaporated to remove water. The concentrated residue was dried further over $MgSO_4$, filtered, followed by flash column chromatography (MeOH:CH_2Cl_2 1:9). 22 g (99%) of the lactone (3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyl-3H-4,5,6-trihydropyran-2-one was obtained. To a solution of the lactone (1.5 g, 9.3 mmol) in pyridine (3 mL) was added benzoyl chloride (3.33 mL, 28.7 mmol) at 0 °C. The mixture was allowed to reach rt and was kept for 30 min. An extractive workup with ether and brine was carried out, and the concentrated residue was purified by silica gel column chromatography (EtOAc:hexanes 3:7) to afford 4.4 g of (3*R*,4*R*,5*R*,6*S*)-6-methyl-2-oxo-4,5-diphenylcarbonyloxy-3H-4,5,6-trihydropyran-3-yl benzoate (100%). To a solution of this tribenzoate (4.2 g, 8.9 mmol) and 10% Pd/C (350 mg) in EtOAc (25 mL) equipped with a H_2 balloon was added TEA (1.85 mL, 13.3 mmol) at rt. The resulting suspension was stirred for 1 day and filtered through Celite with EtOAc and concentrated in vacuo. Flash column chromatography (EtOAc:hexanes 1:4) provided 3.1 g of (3*R*,5*R*,6*S*)-6-methyl-2-oxo-5-phenylcarbonyloxy-3H-4,5,6-trihydropyran-3-yl benzoate as a foaming solid (99%). The dibenzoate (2.1 g, 5.9 mmol) was treated with NaOMe (0.5 M in MeOH, 40 mL) and stirred for 30 min. MeOH was evaporated in vacuo, followed by the addition of 1,4-dioxane (100 mL) and H_2SO_4 (50% aq. 4 mL). The mixture was dried over $MgSO_4$, filtered through Celite, and concentrated. Column chromatography (MeOH:CH_2Cl_2 1:9) gave rise to diol **8** (750 mg, 87%): $[\alpha]^{20}_D$ +2.2 (*c* 1.2, water); IR (neat) 3379, 1770, 1125 cm^{-1}; ^{1}H NMR (400 MHz, MeOH-d_4) δ 4.54 (dd, 1H, *J* = 10.8, 8.7 Hz), 4.27 (quintet, 1H, *J* = 4.7 Hz), 3.98−3.92 (m, 1H), 2.55 (ddd, 1H, *J* = 12.3, 8.6, 5.6 Hz), 2.05 (q, 1H, *J* = 10.6 Hz), 1.17 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, MeOH-d_4) δ 179.3, 81.3, 69.5, 68.4, 32.8, 18.8; HRMS (FAB+) *m*/*z* calcd for $C_6H_{10}O_4$ (M + H) 147.0657, found 147.0807.

(3*R*,5*R*)-5-((1*S*)-1-Hydroxyethyl)-2-oxo-3-3,4,5-trihydrofuryl 6-Methoxy-2-prop-2-enylbenzoate (46). To a solution of **8** (86 mg, 0.59 mmol) in CH_2Cl_2 (5 mL) was added a mixture of DMAP (89 mg, 0.71 mmol), EDCI (136 mg, 0.71 mmol), and **13** (136 mg, 0.71 mmol) in CH_2Cl_2 (2 mL) at 0 °C, and the reaction mixture was stirred for 5 h at rt. Additional DMAP (89 mg, 0.71 mmol), EDCI (136 mg, 0.71 mmol), and **13** (136 mg, 0.71 mmol) in CH_2Cl_2 (2 mL) was added to drive the reaction to completion. After 9 h, the solvent was evaporated and the crude mixture was purified by column chromatography (MeOH/CH_2Cl_2 1:19) to produce 170 mg (90%) of desired ester **46**: $[\alpha]^{20}_D$ +12 (*c* 1.0, $CHCl_3$); IR (neat) 3453, 1793, 1736, 1268, 1118 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, 1H, *J* = 8.1 Hz), 6.85 (d, 1H, *J* = 7.7 Hz), 6.80 (d, 1H, *J* = 8.4 Hz), 5.93 (ddq, 1H, *J* = 16.8, 10.2, 6.6 Hz), 5.72 (dd, 1H, *J* = 10.5, 9.1 Hz), 5.10−5.05 (m, 2H), 4.40 (ddd, 1H, *J* = 9.9, 5.7, 3.5 Hz, 1H), 4.19 (dq, 1H, *J* = 6.4, 3.4 Hz), 3.83 (s, 3H), 3.45 (dq, 2H, *J* = 15.6, 6.6 Hz), 2.76 (ddd, 1H, *J* = 12.6, 8.9, 5.9 Hz), 2.44 (dt, 1H, *J* = 12.5, 10.4 Hz), 2.14 (bs, 1H), 1.20 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 166.9, 156.8, 139.1, 136.2, 131.1, 121.8, 122.7, 116.5, 109.0, 79.8, 69.1, 66.5, 56.0, 37.4, 27.9, 17.3; HRMS (FAB+) *m*/*z* calcd for $C_{17}H_{21}O_6$ (M + H) 321.1338, found 321.1326.

(2*R*,3*R*,5*R*)-5-((1*S*&1*R*)-1-Hydroxyethyl)-2-methoxyoxolan-3-yl 6-Methoxy-2-prop-2-enylbenzoate (47). To a solution of **46** (1.2 g, 3.75 mmol) in toluene (10 mL) under argon atmosphere was slowly added diisobutylaluminum hydride (7.9 mL, 1 M in toluene, 7.9 mmol) at −78 °C. After 15 min, MeOH (5 mL) was added to quench the reaction at −78 °C, followed by the addition of 4 N HCl in dioxane (20 mL) at rt. The reaction was stirred for an additional 8 h. Water (5 mL) was then added, and the majority of the solvents were removed under reduced pressure. Extractive workup with CH_2Cl_2 and aqueous $NaHCO_3$ followed by column chromatography (EtOAc:hexanes 4:1) provided 934 mg of **47** (74%): $[\alpha]^{20}_D$ −28 (*c* 0.90, $CHCl_3$); IR (neat) 3461, 1728, 1267, 1107, 1071 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, two anomers) δ 7.31−7.26 (m, 1H), 6.84−6.77 (m, 2H), 5.96−5.86 (m, 1H), 5.27 (d, 0.6H, *J* = 5.6 Hz), 5.16 (s, 0.4H), 5.08−5.03 (m, 2.6H), 4.65 (s, 0.4H), 4.12 (ddd, 0.6H, *J* = 8.5, 5.8, 2.9 Hz), 4.08−4.02 (m, 0.6H), 3.82 (s, 3H), 3.66−3.54 (m, 0.8H), 3.42 (s, 1.2H), 3.38 (s, 1.8H), 3.42−3.68 (m, 2H), 2.40 (0.6 H, quintet, *J* = 7.4 Hz), 2.25−2.22 (m, 0.4H), 2.22 (s, 0.6H), 2.06 (dd, 0.6H, *J* = 13.3, 4.8 Hz), 1.93 (ddd, 0.4H, *J* = 13.8, 10.8, 3.1 Hz), 1.50 (d, 0.4H, *J* = 5.5 Hz), 1.27 (d, 1.2H, *J* = 5.7 Hz), 1.13 (d, 1.8H, *J* = 6.51 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, two anomers) δ 167.8, 167.6, 157.1, 157.1, 139.3, 139.0, 136.8, 136.7, 131.2, 131.0, 123.7, 123.2, 122.3, 122.1, 116.8, 116.7, 109.5, 109.5, 107.0, 97.6, 82.4, 78.5, 71.7, 69.6, 68.5, 67.6, 56.3, 56.3, 55.2, 55.0, 37.9, 33.1, 29.0, 18.8, 18.0; HRMS (FAB+) *m*/*z* calcd for $C_{18}H_{25}O_6$ (M + H) 337.1651, found 337.1644.

(3*R*,5*R*)-5-((1*S*)-1-Methylbut-3-enyl)-2-methoxyoxolan-3-yl 6-Methoxy-2-prop-2-enylbenzoate (49). To a solution of **47** (49 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) were added at 0 °C pyridine (0.025 mL, 0.29 mmol) and triflic anhydride (0.037 mL, 0.22 mmol). After 5 min of stirring, the mixture was quenched with saturated $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (50 mL). The organic layer was dried over $MgSO_4$, concentrated, and filtered through Celite. The crude triflate **48** was dried under vacuum at 0 °C for 1 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, 1H, *J* = 8.0 Hz), 6.82 (d, 1H, *J* = 7.5 Hz), 6.79 (d, 1H, *J* = 8.4 Hz), 5.90 (ddt, 1H, *J* = 16.9, 10.2, 6.5 Hz, 1H), 5.30 (dd, 1H, *J* = 6.8, 2.1 Hz, 1H), 5.11−5.04 (m, 3H), 5.01 (q, 1H, *J* = 1.7 Hz), 4.26 (ddd, 1H, *J* = 9.5, 5.0, 4.7 Hz), 3.81 (s, 3H), 3.41 (s, 3H), 3.36 (d, 2H, *J* = 6.5 Hz), 2.63 (ddd, 1H, *J* = 14.4, 8.2, 7.0 Hz), 1.96 (ddd, 1H, *J* = 14.3, 6.0, 2.1 Hz), 1.52 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 157.1, 138.9, 136.6, 131.2, 123.1, 122.1, 116.8, 109.4, 107.8, 87.3, 79.1, 77.9, 77.6, 56.2, 55.3, 37.8, 32.0, 17.4. In another flask, CuCN (25 mg, 0.29 mmol) was heated under vacuum for 5 min and suspended in anhydrous THF (20 mL) at −78 °C. MeLi (0.36 mL, 1.6 M in Et_2O, 0.58 mmol) was added slowly. The mixture was allowed to reach 0 °C, then allyltributyltin (0.18 mL, 0.58 mmol) was added, and the resulting solution was stirred for 30 min. After being cooled to −78 °C, the mixture was added to a solution of the triflate **48** in THF (5 mL) at −90 °C. After being stirred for 1 h, the reaction mixture was quenched by careful addition of concentrated aqueous NH_4OH solution saturated with NH_4Cl (10 mL) and stirred at rt overnight. Extractive workup with ether followed by column chromatography (EtOAc:hexanes 1:19) gave 16 mg (30% for two steps) of allylated product **49**: $[\alpha]^{20}_D$ −16 (*c* 0.80, $CHCl_3$); IR (neat) 1731, 1267, 1107, 1070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, α-anomer) δ 7.28 (t, 1H, *J* = 8.2 Hz), 6.82 (d, 1H, *J* = 7.8 Hz), 6.77 (d, 1H, *J* = 8.3 Hz), 5.94 (ddt, 1H, *J* = 17.0, 10.1, 6.7 Hz), 5.81 (dddd, 1H, *J* = 17.4, 9.7, 7.8, 6.7 Hz), 5.17 (ddd, 1H, *J* = 11.0, 7.9, 4.2 Hz), 5.12−

5.01 (m, 5H), 3.86−3.80 (m, 1H), 3.82 (s, 3H), 3.40 (s, 3H), 3.40−3.39 (m, 2H), 2.47−2.42 (m, 1H), 2.37 (ddd, 1H, J = 11.8, 7.8, 6.4 Hz), 2.02−1.90 (m, 2H), 1.74−1.70 (m, 1H), 0.83 (d, 3H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, α-anomer) δ 167.6, 157.1, 138.9, 136.7, 131.0, 123.6, 122.1, 116.7, 109.4, 97.6, 71.7, 69.5, 68.4, 56.3, 56.2, 55.1, 37.8, 32.9, 18.0; ^{1}H NMR (400 MHz, $CDCl_3$, β-anomer) δ 7.29 (t, 1H, J = 8.0 Hz), 6.82 (d, 1H, J = 7.6 Hz), 6.77 (d, 1H, J = 8.3 Hz), 5.90 (ddt, 1H, J = 17.7, 9.5, 6.6 Hz), 5.79 (dddd, 1H, J = 17.5, 9.7, 7.7, 6.6 Hz), 5.27 (dd, 1H, J = 7.2, 2.8 Hz), 5.07−5.00 (m, 5H), 3.93 (q, 1H, J = 7.6 Hz), 3.81 (s, 3H), 3.37 (s, 3H), 3.37−3.35 (m, 2H), 2.52 (dt, 1H, J = 13.9, 7.3 Hz), 2.39−2.33 (m, 1H), 1.99−1.89 (m, 1H), 1.82−1.77 (m, 1H), 1.73 (ddd, 1H, J = 14.1, 7.5 Hz), 0.87 (d, 3H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, β-anomer) δ 167.5, 156.6, 138.4, 136.6, 136.2, 130.6, 123.2, 122.6, 116.4, 116.2, 109.0, 106.6, 81.4, 79.0, 55.8, 54.3, 37.7, 37.4, 37.4, 33.8, 29.7, 14.9; HRMS (ES+) *m/z* calcd for $C_{21}H_{32}N_1O_5$ (M + NH_4) 378.2280, found 378.2293.

(3*R*,5*R*)-5-((1*S*&1*R*)-1-Methylbut-3-enyl)-2-hydroxyoxolan-3-yl 6-Hydroxy-2-prop-2-enylbenzoate (50). To a solution of **49** (77 mg, 0.21 mmol) in CH_2Cl_2 (6 mL) was added BCl_3 (1 M in CH_2Cl_2, 2.0 mL) at −78 °C, and the mixture was stirred for 30 min. Water was added to stop the reaction. Extractive workup with CH_2Cl_2 (50 mL) and subsequent column chromatography (EtOAc:hexanes 1:3) gave 34 mg (48%) of **50** as a mixture of anomers: $[\alpha]^{20}_D$ −1.0 (*c* 0.40, $CHCl_3$, 24 h); IR (neat) 3417, 1660, 1607, 1450 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.0 (s, 0.75H), 10.6 (s, 0.25H), 7.34 (t, 0.75H, J = 7.9 Hz), 7.33 (t, 0.25H, J = 7.8 Hz), 6.90−6.87 (m, 1H), 6.77−6.74 (m, 1H), 6.05 (ddt, 0.25H, J = 17.1, 10.3 6.0 Hz), 5.98 (ddt, 0.75H, J = 17.1, 10.3, 6.0 Hz), 5.83−5.74 (m, 1H), 5.58 (d, 0.75H, J = 1.6 Hz), 5.54 (t, 0.25H, J = 4.4 Hz), 5.35 (dd, 0.75H, J = 7.2, 3.1 Hz), 5.27 (ddd, 0.25H, J = 9.9, 7.7, 4.3 Hz), 5.06−4.91 (m, 4H), 4.14 (q, 0.75H, J = 7.6 Hz), 3.85−3.80 (m, 0.25H), 3.74−3.64 (m, 2H), 3.11 (d, 0.25H, J = 4.7 Hz), 2.79 (d, 0.75H, J = 2.3 Hz), 2.61 (dt, 0.75H, J = 14.1, 7.3 Hz), 2.46−2.35 (m, 1.25H), 2.05−1.91(m, 1.25H), 1.82−1.76 (m, 1.75H), 0.89 (d, 3H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 170.1, 163.3, 162.3, 143.1, 143.1, 138.3, 137.9, 136.8, 136.8, 123.1, 123.0, 116.8, 116.7, 116.7, 116.0, 115.9, 112.8, 112.1, 100.9, 94.6, 82.3, 81.1, 80.7, 75.1, 40.5, 40.1, 39.5, 38.1, 38.1, 38.0, 34.1, 31.5, 15.4, 15.1; HRMS (FAB+) *m/z* calcd for $C_{19}H_{25}O_5$ (M + H) 333.1702, found 333.1717.

1-((1*E*&1*Z*)-2-Cyanovinyl)(4*S*,1*R*,3*R*)-3-hydroxy-4-methylhept-6-enyl 6-Hydroxy-2-prop-2-enylbenzoate (51). To a solution of **50** (58 mg, 0.17 mmol) in toluene (5 mL) was added (triphenylphosphoranylidene)-acetonitrile (68 mg, 0.23 mmol), and the mixture was stirred at 80 °C for 1 h. After cooling, the solution was directly loaded on a silica gel column. Column chromatography (EtOAc:hexanes 3:7) afforded 65 mg (98%, *E*:*Z* 23:2) of acryl nitrile **51**: $[\alpha]^{20}_D$ −10 (*c* 0.20, $CHCl_3$); IR (neat) 3451, 3075, 2228, 1661, 1606, 1450, 1216 cm^{-1}. *E*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.9 (s, 0.08H), 10.8 (s, 0.92H), 7.38 (t, 1H, J = 7.9 Hz), 6.92 (d, 0.92H, J = 8.3 Hz), 6.88 (d, 0.08H, J = 8.3 Hz), 6.54 (dd, 0.08H, J = 11.5, 8.1 Hz), 6.03−5.93 (m, 2H), 5.78 (ddt, 1H, J = 17.0, 10.0, 7.2 Hz), 5.62 (d, 0.92H, J = 16.4 Hz), 5.52 (d, 0.08H, J = 11.0 Hz), 5.08−5.02 (m, 3H), 4.89 (dd, 1H, J = 17.2, 1.3 Hz), 3.68 (d, 2H, J = 5.5 Hz), 3.61−3.54 (m, 1H), 2.23 (t, 1H, J = 13.3, 6.1 Hz), 2.03 (d, 1H, J = 4.8 Hz), 2.00−1.93 (m, 2H), 1.78 (ddd, 1H, J = 13.9, 10.7, 3.0 Hz), 1.68 (quintett, 1H, J = 6.8 Hz), 0.92 (d, 2.76H, J = 6.8 Hz), 0.89 (d, 0.24H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, *E*-isomer) δ 170.4, 162.9, 151.2, 142.2, 137.4, 136.6, 135.1, 123.0, 116.7, 116.3, 115.9, 111.5, 101.4, 71.7, 71.0, 40.0, 38.9, 38.0, 37.8, 37.1, 15.2; HRMS (ES+) *m/z* calcd for $C_{21}H_{26}N_1O_4$ (M + H) 356.1862, found 356.1875.

(1*S*,3*R*,4*S*)-1-(2-Cyanoethyl)-3-hydroxy-4-methylhept-6-enyl 6-Hydroxy-2-prop-2-enyl-benzoate (52). To a solution of **51** (15 mg, 0.04 mmol) in benzene (10 mL) was added $[Ph_3PCuH]_6$ (41 mg, 0.02 mmol) at 0 °C. The solution was allowed to reach rt and was stirred for an additional 10 min. Evaporation of the solvent and column chromatography (EtOAc:hexanes 1:3) afforded the saturated nitrile **52** (12 mg, 80%): $[\alpha]^{20}_D$ −15 (*c* 0.30, $CHCl_3$); IR (neat) 3446, 3076, 2926, 2249, 1656, 1606, 1450, 1249, 1220, 1120, 914, 817 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.0 (s, 1H), 7.36 (t, 1H, J = 7.9 Hz), 6.91 (d, 1H, J = 8.2 Hz), 6.8 (d, 1H, J = 7.42 Hz), 5.99 (ddt, 1H, J = 17.1, 10.3, 5.6 Hz), 5.8 (ddt, 1H, J = 17.1, 9.9, 7.2 Hz), 5.54 (ddt, 1H, J = 9.0, 6.1, 2.8 Hz), 5.07−4.98 (m, 3H), 4.88 (dq, 1H, J = 17.2, 1.6 Hz), 3.67 (d, 2H, J = 5.5 Hz), 3.48 (s, 1H), 2.51−2.39 (m, 3H), 2.44 (dt, 1H, 13.8, 6.0 Hz), 2.14 (q, 2H, J = 7.3 Hz), 1.97−1.87 (m, 2H), 1.69 (ddd, 1H, J = 13.9, 10.8, 2.7 Hz, 1H), 1.67−1.61 (m, 1H), 0.89 (d, 3H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 162.9, 142.2, 137.5, 136.8, 134.8, 123.0, 118.7, 116.6, 116.4, 115.6, 111.6, 72.3, 71.0, 40.0, 38.8, 38.4, 37.0, 30.9, 15.1, 13.9; HRMS (FAB+) *m/z* calcd for $C_{21}H_{28}N_1O_4$ (M + H) 358.2018, found 358.1999.

(1*S*,3*S*,4*S*)-1-(2-Cyanoethyl)-4-methyl-3-(1,1,2,2-tetramethyl-1-silapropoxy)hept-6-enyl 2-Prop-2-enyl-6-(1,1,2,2-tetramethyl-1-silapropoxy)benzoate (53). To a solution of **52** (35 mg, 0.1 mmol) in CH_2Cl_2 (5 mL) were added pyridine (0.08 mL, 0.98 mmol) and TBSOTf (0.18 mL, 0.78 mmol) at 0 °C, and the mixture was stirred for 5 h. The solvent was removed in vacuo, and the residue was subjected to column chromatography (EtOAc:hexane 1:9) to result in 52 mg of compound **53** (91%): $[\alpha]^{20}_D$ +10 (*c* 0.50, $CHCl_3$); IR (neat) 2244, 1726, 1583, 1465, 1255, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, 1H, J = 7.91 Hz), 6.81 (d, 1H, J = 7.7 Hz), 6.74 (d, 1H, J = 8.2 Hz), 5.92 (ddt, 1H, J = 16.8, 10.2, 6.4 Hz), 5.75 (ddt, 1H, J = 7.01, 10.04, 17.04 Hz, 1H), 5.10−4.96 (m, 5H), 3.87 (dt, 1H, J = 9.1, 2.8 Hz), 3.38−3.29 (m, 2H), 2.44 (ddq, 1H, J = 16.4, 10.0, 5.6 Hz), 2.22−2.13 (m, 1H), 2.10−2.02 (m, 2H), 1.88−1.80 (m, 2H), 1.78−1.68 (m, 1H), 1.59 (ddd, 1H, J = 14.4, 9.1, 5.7 Hz), 0.98 (s, 9H), 0.91 (s, 9H), 0.88 (d, 3H, J = 6.7 Hz), 0.25 (s, 3H), 0.24 (s, 3H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 152.9, 138.5, 137.4, 136.5, 130.5, 126.5, 122.3, 119.5, 117.4, 117.0, 116.4, 73.2, 73.0, 39.4, 37.9, 37.7, 36.5, 31.5, 26.3, 26.2, 18.8, 18.4, 13.9, 13.8, −3.6, −3.7, −3.8, −3.9; HRMS (ES+) *m/z* calcd for $C_{33}H_{56}N_1O_4Si_2$ (M + H) 586.3748, found 586.3738.

3-[(3*S*,5*R*,6*S*)-5,14-Bis(1,1,2,2-tetramethyl-1-silapropoxy)-6-methyl-1-oxo-2,3,4,5,6,7,10-heptahydrobenzo[*d*]-[12]annulen-3-yl]propanenitrile (*E*-54 from 53). To a solution of **53** (52 mg, 0.09 mmol) in CH_2Cl_2 (20 mL) was added Grubbs I catalyst (3.7 mg, 0.0045 mmol), and the solution was heated at reflux temperature for 12 h. Catalyst (3.7 mg, 0.0045 mmol) was added every 1 h for another three times, and after completion of the reaction the solvent was removed under reduced pressure. Column chromatography (EtOAc:hexane 1:19) gave 40 mg (81%) of the *E*-isomer **54** and 17% of the *Z*-isomer. *E*-**54**: $[\alpha]^{20}_D$ +2.5 (*c* 1.2, $CHCl_3$); IR (neat) 2249, 1726, 1255, 1055 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (t, 1H, J = 7.9 Hz), 6.76 (d, 1H, J = 8.3 Hz), 6.74 (d, 1H, J = 8.8 Hz), 5.44−5.31 (m, 2H), 5.20 (q, 1H, J = 6.3 Hz), 4.26 (dd, 1H, J = 8.2, 3.2 Hz, 1H), 3.66 (dd, 1H, J = 16.4, 9.5 Hz, 1H), 3.33 (ddt, 1H, J = 16.2, 3.3, 1.8 Hz), 2.45 (ddq, 2H, J = 16.6, 9.4, 6.5), 2.28 (d, 1H, J = 12.0 Hz), 2.07−2.07 (m, 2H), 1.82 (oct, 1H, J = 5.5 Hz), 1.74 (dd, 1H, J = 15.1, 8.3 Hz), 1.69 (q, 1H, J = 11.7 Hz), 1.33 (dd, 1H, J = 14.9, 9.1 Hz, 1H), 0.98 (s, 9H), 0.92 (s, 9H), 0.84 (d, 3H, J = 6.75 Hz), 0.24 (s, 3H), 0.19 (s, 3H), 0.16 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 153.1, 139.0, 131.7, 130.0, 128.6, 127.6, 123.8, 119.6, 118.6, 72.8, 72.2, 38.5, 37.2, 32.5, 26.3, 26.2, 18.8, 18.4, 13.9, 13.4, −3.6, −4.0, −4.0, −4.1; HRMS (FAB+) *m/z* calcd for $C_{31}H_{52}N_1O_4Si_2$ (M + H) 558.3435, found 558.3442. *Z*-**54**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, 1H, J = 7.9 Hz), 6.79 (d, 1H, J = 7.5 Hz), 6.74 (d, 1H, J = 8.2 Hz), 5.36−5.26 (m, 3H), 3.99 (d, 1H, J = 8.4 Hz), 3.90 (dd, 1H, J = 15.7, 8.5 Hz), 3.01 (d, 1H, J = 15.2 Hz), 2.41−2.31 (m, 2H), 2.08−1.95 (m, 3H), 1.90−1.85 (m, 2H), 1.75−1.70 (m, 1H), 1.49 (dd, 1H, J = 15.0, 8.9 Hz), 0.97 (s, 9H), 0.90 (s, 9H), 0.90 (m, 3H), 0.25 (s, 3H), 0.24 (s, 3H), 0.19 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 153.7, 140.4, 130.8, 129.4, 129.1, 126.3, 123.4,

119.4, 117.7, 72.3, 70.7, 39.9, 38.8, 33.0, 32.2, 30.1, 26.3, 26.0, 14.2, 13.3, −3.7, −4.1, −4.1, −4.3.

3-[(3*S*,5*R*,6*S*)-5,14-Bis(1,1,2,2-tetramethyl-1-silapropoxy)-6-methyl-1-oxo-2, 3,4,5,6,7,10-heptahydrobenzo[*d*][12]-annulen-3-yl]propanenitrile (*E*-54 from 23). A solution of **23** (33 mg, 0.10 mmol), TBSOTf (0.23 mL, 1.0 mmol), and pyridine (1 mL) in CH_2Cl_2 (6 mL) was stirred for 4 h. The mixture was directly loaded on a silica gel column. Column chromatography (EtOAc:hexane 1:9) afforded 54 mg (97%) of **54**. For data, refer to the previous synthesis of **54** above.

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Supporting Information Available: Copies of ^{1}H NMR spectra for compounds **8**−**12**, **14**−**23**, **25**−**54**. Copies of ^{13}C NMR spectra for compounds **8**−**12**, **14**−**18**, **20**−**23**, **25**−**37**, **46**−**54**. HPLC traces for compounds **21**, **38**−**45**. This material is available free of charge via the Internet at http://pubs.acs.org.

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