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Formal Total Synthesis of (+)-Salicylihalamides A and B: A Combined Chiral Pool and RCM Strategy

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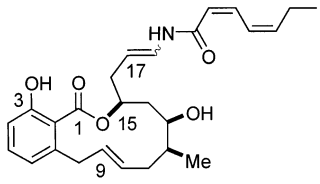
The formal total synthesis of the (+)-salicylihalamides A and B is detailed, utilizing a chiral pool approach to generate the three stereogenic centers and a ring-closing metathesis (RCM) for the formation of the macrocyclic ring structure. Starting from a known glucose-derived alcohol, the formal total synthesis was achieved in an efficient 13-step protocol in 26% overall yield. It was found that substitution at the remote phenolic group significantly influenced the ratio of the *E*- and *Z*-double bond products in the RCM step. The introduction of phenol protecting groups provided *E*-isomers preferentially and also enhanced the rates of the RCM reactions.

Introduction

The salicylihalamides (Figure 1) are naturally occurring cytotoxic macrolides, sharing a medium-sized macrolide ring bearing a salicylate moiety and a dienylenamide side chain. Isolated from an Australian sponge of the genus *Haliclona*, they were the first examples of a novel class of compounds showing a striking pattern of differential cytotoxicity in the NCI 60-tumor cell line screen[1,2] with a mean panel GI_{50} of approximately 15 nM.[3] Due to their unique profile in the COMPARE pattern recognition analysis,[4,5] it was proposed that they act by a novel mechanism of action.[3] Further COMPARE analyses implicated the V-type (H+) ATPases as a molecular target.[6] It is now known that the salicylihalamides inhibit the mammalian V-ATPases with unprecedented selectivity.[6] The V-type ATPase-mediated regulation of the intracellular pH in eukaryotic cells[7] is important for cellular activities such as the sorting of membrane and organellar proteins, neurotransmitter uptake, cellular degradative processes, and receptor recycling. Abnormal V-ATPase function is implicated in several disease states including osteoporosis and cancer.[8,9]



(-)-salicylihalamide A, 17-*E*
(-)-salicylihalamide B, 17-*Z*

FIGURE 1. Structures of salicylihalamides A and B.

Since the discovery of the salicylihalamides in 1997, a growing number of structurally related natural products have been reported, among them the lobatamides A−F,[10−12] oximidines I and II,[13] apicularens A and B,[14,15] and CJ-12,950 and CJ-13,357.[16]

Due to their unique architecture and intriguing biological activity, the class of the benzolactone enamides has received considerable attention. Several total syntheses of salicylihalamides,[17−25] apicularen A,[25−28] and

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lobatamide C[29,30] have been reported as well as studies on the synthesis of the macrocyclic core[31−37] and the enamide side chain.[38−41] The initially proposed absolute stereochemistry of the salicylihalamides was revised by total synthesis and is now assigned as shown in Figure 1 (12*S*,13*R*,15*S*).[17,42]

Retrosynthetic Analysis. Since we commenced our synthetic effort at a time when the stereochemistry of the naturally occurring (−)-salicylihalamides had been assigned incorrectly,[17,42] our initial focus was the completion of the total synthesis of the (+)-salicylihalamides A and B. The two main synthetic challenges associated with these target molecules are the efficient synthesis of the 12-membered macrocycle, in particular the geometry and the regiochemistry of the double bond, as well as the introduction of the labile enamide side chain. We reasoned that the sensitive enamide functionality would be best installed at a very late stage of our synthetic approach, leading to key intermediate **2**.[23] The synthesis of the macrocyclic aldehyde **2** following an enantioselective route was first reported by the Labrecque group in their total synthesis of (+)- and (−)-salicylihalamides A and B.[23]

Our synthetic strategy (Figure 2) for the preparation of core structure **2** involves the use of the aromatic component allylsalicylic acid **5** and readily available diacetone-D-glucose **8**, the chiral source for the required stereocenters, as our two building blocks. Formation of the C9 to C10 alkene[43] through ring-closing metathesis (RCM)[44−48] provides an attractive solution for the construction of the macrocyclic core structure and has been

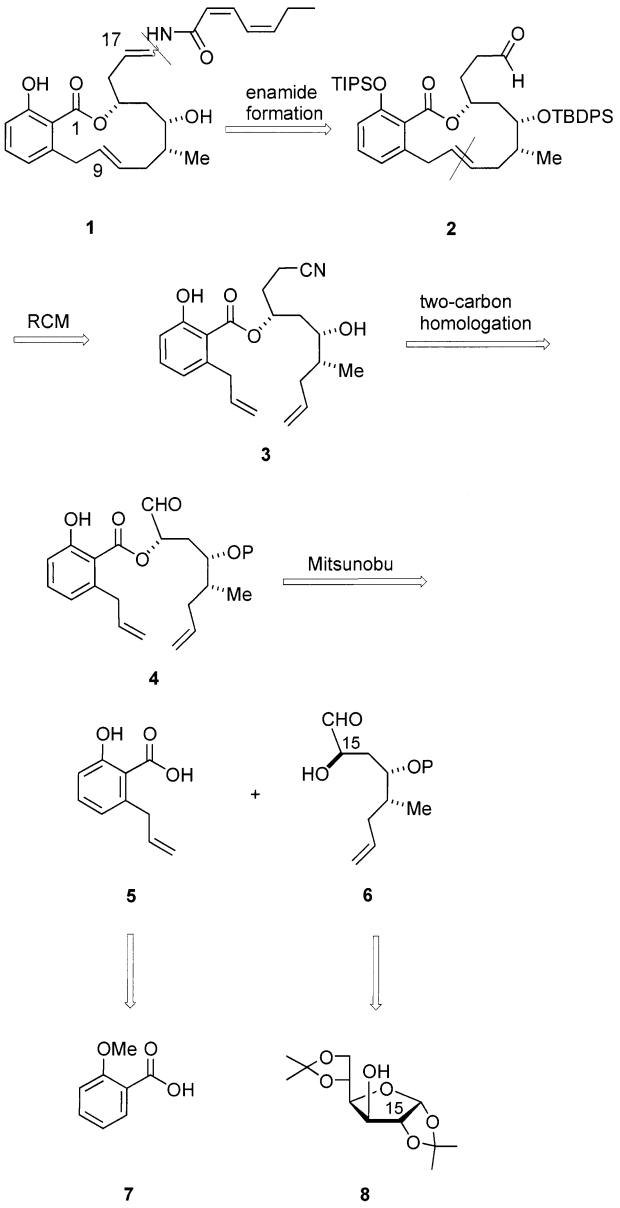

FIGURE 2. Retrosynthetic analysis for the salicylihalamides.

successfully employed in nearly all reported total[17,21−24] and partial[18,31,49,50] syntheses of the salicylihalamides. The RCM precursor, nitrile **3**, is accessible via Mitsunobu esterification of **6** with 2-allylsalicylic acid (**5**) followed by a two-carbon homologation step. Although building block **6** is accessible by various asymmetric routes, pursuing a chiral pool approach seemed particularly appealing to us, because it would not require separation of diastereoisomers and the reactions could be scaled up easily.

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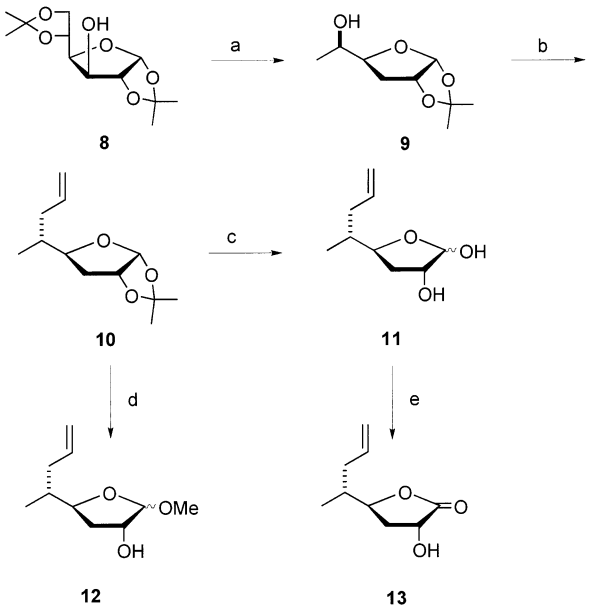
SCHEME 1[a]



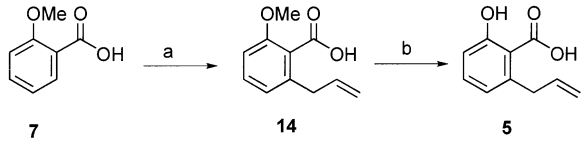
[a] Reagents and conditions: (a) refs 51−53. (b) (i) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min to 1 h; (ii) $(CH_2{=}CHCH_2)_2Cu(CN)Li_2$, THF, −78 °C, 30 min, 84%. (c) 70% aq acetic acid, 50 °C, 5 h, 83%. (d) MeOH, HCl, dioxane, rt, 1 h, 95%. (e) Ag_2CO_3/Celite, benzene, 80 °C, 1 h, 95%.

Results and Discussion

The starting point for the macrolide synthesis was the alcohol **9** (Scheme 1), which was prepared from diacetone-D-glucose **8** in five steps.[51−53] The secondary hydroxyl group of **9** was converted to its corresponding triflate and used immediately, without purification, in the next step. Reaction of the triflate with a higher order allylcyanocuprate[54] provided allylated intermediate **10** with complete inversion of stereochemistry in 84% yield. Initial attempts to achieve this conversion employing the mesylate, tosylate, or imidazolate of alcohol **9** were unsuccessful. Deprotection of the acetonide functionality of **10** was carried out with 70% acetic acid to yield alcohol **11**. Methanolysis of **10** gave rise to the cyclic hemiacetal **12**.

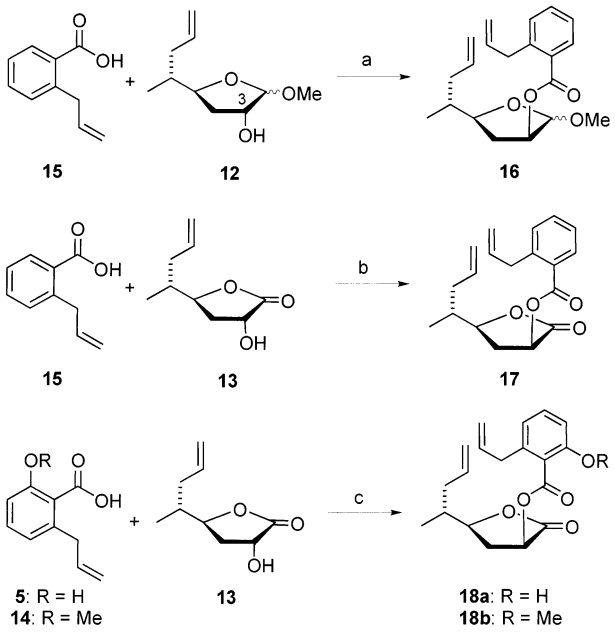
The salicylic acid moiety **5** was prepared in a two-step sequence utilizing commercially available *O*-methylsalicylic acid **7** (Scheme 2). Ortho-metalation[55−57] of **7** with *sec*-BuLi at low temperature followed by trapping of the resulting bislithium anion with allyl bromide gave rise to 2-allyl-6-methoxybenzoic acid **14** in moderate yield. Cleavage of the aromatic methyl ether was accomplished by reaction with BCl_3/$(n\text{-Bu})_4NI$,[58] providing the key intermediate **5** in 38% overall yield.

SCHEME 2[a]



[a] Reagents and conditions: (a) *sec*-BuLi, TMEDA, THF, allyl bromide, −90 °C to rt, 46%. (b) BCl_3, $(n\text{-Bu})_4NI$, CH_2Cl_2, −78 °C to rt, 90%.

SCHEME 3[a]



[a] Reagents and conditions: (a) Ph_3P, DEAD, 90 °C, benzene or toluene, 7 h, 17% (50% starting material recovered). (b) Ph_3P, DEAD, rt, toluene, 1 h, 87%. (c) (i) R = H; Ph_3P, DEAD, −78 °C to rt, THF, 5 h, 90%; (ii) R = Me; Ph_3P, DEAD, −78 °C to rt, THF, 5 h, 98%.

Preliminary model studies (Scheme 3) addressing the esterification and concomitant inversion of the stereogenic center at C3 (C15 salicylihalamide numbering) of the cyclic hemiacetal **12** with 2-allylbenzoic acid **15**[59,60] under Mitsunobu conditions in benzene or toluene at elevated temperatures resulted only in low yields of **16**. On the contrary, lactone **13**, obtained in good yield by selective oxidation of lactol **11** with Ag_2CO_3/Celite (Scheme 1),[61] furnished the ester **17** in 87% yield at room temperature. Oxidation of the lactol to the corresponding lactone, which leads to a more rigid ring system, presumably decreases the steric hindrance at position 3, and increases the electrophilicity of this carbon, hence facilitating a nucleophilic attack. Analogously, the esterification of the carbohydrate building block **13** with 2-allyl-6-hydroxybenzoic acid (**5**) or 2-allyl-6-methoxybenzoic acid (**14**) under Mitsunobu conditions furnished the intermediates **18a** and **18b** in 90% and 98% yield,

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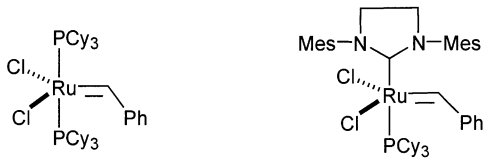
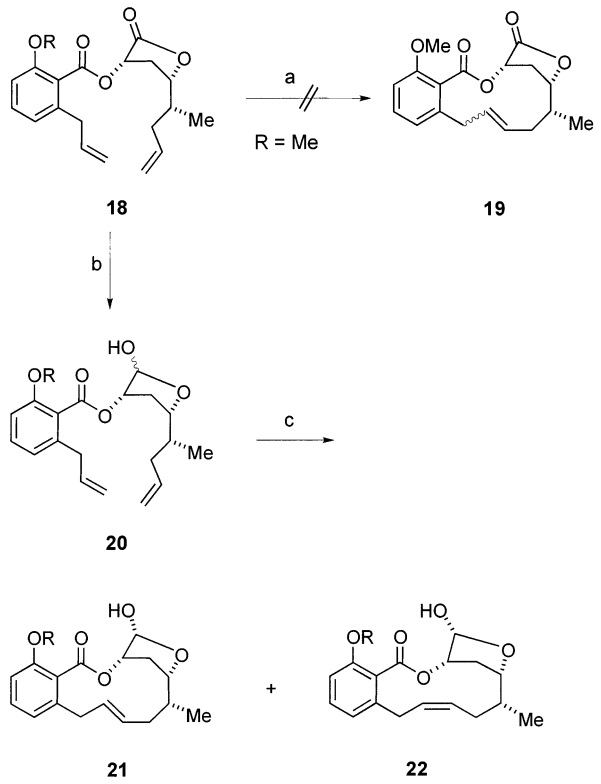


Grubbs 1 **Grubbs 2**

FIGURE 3. Structures of Grubbs catalysts 1 and 2.

SCHEME 4[a]



[a] Reagents and conditions: (a) for R = Me; Grubbs catalyst 1, CH_2Cl_2, reflux, 12 h. (b) DIBAL-H, ether, −78 °C, 30 min, **20a** (82%), **20b** (95%), **20c** (88%), **20d** (90%). (c) Grubbs catalyst 1, CH_2Cl_2, reflux, 12 h (yields see Table 1).

respectively (Scheme 3). In this case THF was selected as a solvent, because the reaction was carried out at −78 °C.

After installing the three stereogenic centers, our next objective was the regioselective introduction of the trans $\Delta^{9,10}$ alkene via RCM.

RCM Studies

Surprisingly, all attempts subjecting lactone **18b** to RCM reaction conditions (10 mol % of Grubbs catalyst 1 (Figure 3), CH_2Cl_2, reflux, 12 h) hoping to form macrocycle **19** proved to be unsuccessful (Scheme 4). Apparently, the presence of the lactone ring in **18** prevents favorable conformations that allow RCM reactions to take place. Therefore, the lactone moieties of intermediates **18a** and **18b** were selectively reduced with DIBAL-H, rendering the corresponding lactols **20a** (R = H) and **20b** (R = Me). Both were obtained as mixtures of diastereoisomers (1:3, α:*β*).[62] RCM with **20a** and **20b** employing the same reaction conditions as before now provided the desired products. However, in both cases, the *Z*-isomer was found to be the major one (entries 1 and 2, Table 1) with *E*:Z ratios of 15:85 (for *E*-**21a**:*Z*-**22a**) and 43:57 (for *E*-**21b**:*Z*-**22b**), respectively. These results indicated that the substituent at the phenolic 3-hydroxyl group must have had a significant influence on the *E*:*Z* ratio during the RCM reaction. It is of interest to note that reaction products **21** and **22** were isolated as *β*-anomers only,[62] although we had started with a mixture of anomers **20** (1:3 to 1:6 ratio of α- to *β*-anomers). We speculated that most likely the *β*-anomers of **20** were undergoing RCM reaction preferentially and that anomerization of α-**20** to *β*-**20** occurred during the reaction. It is also possible that anomerization of α-**21**,**22** to the corresponding *β*-anomers took place after RCM reaction.

Since we had noted a remote effect of the phenolic substituent on the stereoselectivity of the RCM reaction,[63] we decided to further investigate the influence of phenolic protecting groups on the double bond geometry with respect to our goal of achieving higher *E*-selectivity.

We therefore employed cyclic hemiacetals of type **20**, accessible via **18a** by introducing an appropriate protecting group followed by reduction with DIBAL-H, in the RCM reactions. The results of these studies are shown in Table 1. The RCM reactions were carried out by refluxing substrates **20a**−**20d** in CH_2Cl_2 in the presence of 12 to 26 mol % of Grubbs catalyst 1 for 12 to 21 h, or by refluxing in toluene in the presence of 4 mol % of Grubbs catalyst 2 (Figure 3) for 2 to 4 h.

When the phenolic hydroxyl group in **20a** was replaced by a triisopropylsilyloxy substituent (compound **20c**, entry 3, Table 1), *E*-isomer formation was favored (64:36 ratio of *E*-**21c**:*Z*-**22c**). The best *E*-selectivity was obtained after introducing a TBDPS protecting group (compound **20d**, 75:25 ratio of *E*-**21d**:*Z*-**22d**, entry 4 in Table 1).

After deprotection of the silyl ethers *E*-**21c**,**d** and *Z*-**22c**,**d**, the stereoisomers *E*-**21a** and *Z*-**22a** could be separated by column chromatography, affording, in the case of *E*-**21d** and *Z*-**22d**, the desired pure *E*-isomer *E*-**21a** in 60% yield.

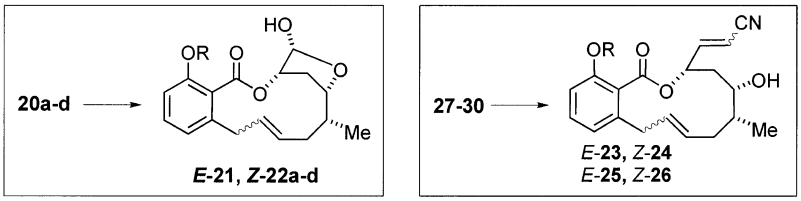
These results demonstrated that the presence of sterically demanding substituents probably either promotes a conformational change of the transition state during the RCM reaction, thus enhancing the formation of the *E*-alkene, or increases the final thermodynamic stability of the *E*- versus the *Z*-isomer.

In our efforts to increase the *E*-selectivity of the RCM reaction, we also explored the more reactive perhydroimidazoline Grubbs 2 catalyst. However, reaction of substrate **20a** with the Grubbs 2 catalyst (entry 5, Table 1) at room temperature provided *Z*-olefin *Z*-**22a** as the sole reaction product. In the case of the TBDPS-protected substrate **20d** (entry 6, Table 1), again *E*-product forma-

(62) The ^{13}C chemical shifts for α-anomeric carbons of furanoses typically resonate at higher field compared to the *β*-anomeric carbons. Pretsch, E.; Seibel, J.; Simon, W.; Clerc, T. *Tables of Spectral Data for Structure Determination of Organic Compounds*; Springer: Berlin, Germany, 1989; p C210.

(63) The influence of remote phenolic substituent on the *E*:*Z* ratio of RCM product formation toward the salicylihalamide macrolactone was also noted by Fürstner et al.[33] and Wu et al.[17] Results of our study were reported earlier.[68]

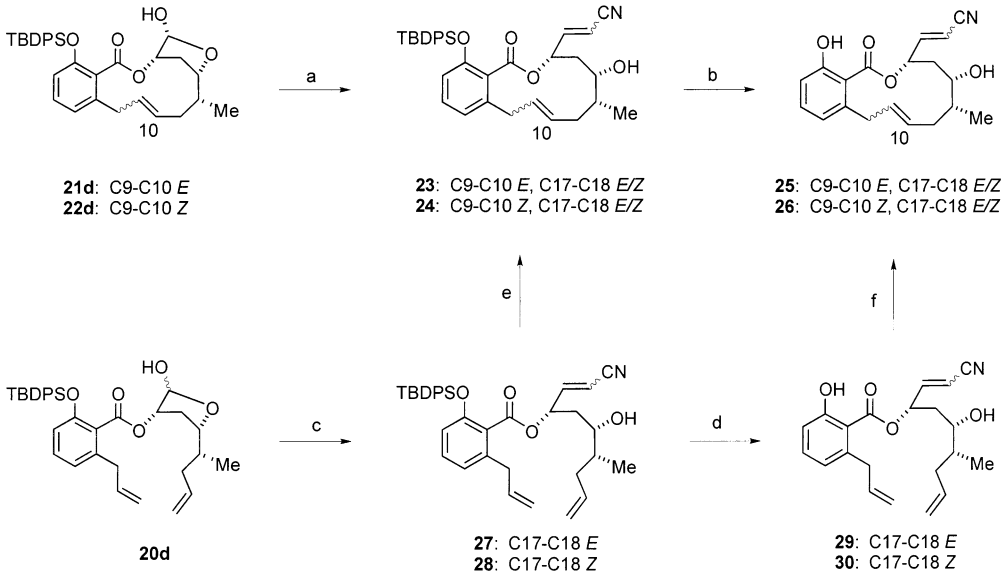
TABLE 1. *E*:*Z* Ratios and Yields for RCM Reactions



entry	compd	R	Grubbs catalyst	*E*:*Z* ratios[a]	yield, %
				E*-21**:Z*-22**	
1	**20a**	H	1	15:85	69
2	**20b**	Me	1	43:57	38
3	**20c**	TIPS	1	64:36[b]	60
4	**20d**	TBDPS	1	75:25[b]	75
5	**20a**	H	2	0:100	59
6	**20d**	TBDPS	2	60:40[b]	80
				23:**24**	
7	**27**, **28**	TBDPS	1	92:8[c]	96
				25:**26**	
8	**29**, **30**	H	1	20:80[c]	33[d]

[a] Ratios determined by ^{1}H NMR. [b] Ratios determined by ^{1}H NMR after removal of the silyl groups. [c] Ratios determined by ^{1}H NMR after removal of the silyl groups and reduction of the C16 double bond. [d] 50% conversion after 1 d.

SCHEME 5[a]



[a] Reagents and conditions: (a) Ph_3P=CHCN, toluene, reflux, 1 h, 68%. (b) TBAF, THF, rt, 20 min, 99%. (c) Ph_3P=CHCN, toluene, reflux, 1 h, 97%. (d) TBAF, THF, 0° to rt, 15 min, 60%. (e) Grubbs catalyst 1, CH_2Cl_2, reflux, 6 h, 96%. (f) Grubbs catalyst 1, CH_2Cl_2, reflux, 1 d, 33%.

tion dominated. The results from these experiments suggest that the thermodynamically more favored isomer is formed in the reaction as the major product and that the reversible nature of the RCM reaction[64,65] can drive the reaction to the energetically most favorable isomer.

Completion of the Formal Total Synthesis

Treating a mixture of lactols **21d**, **22d** with the stabilized ylide (triphenylphosphoranylidene)acetonitrile in refluxing toluene afforded the macrocycles **23** and **24** carrying the masked aldehyde functionality (nitrile) as a mixture of diastereoisomers in high yield (Scheme 5). The same reaction, employing the corresponding aldehyde ylide instead of the nitrile ylide, was low yielding. Due to the fact that the "loss of material" caused by the formation of the undesired *Z*-configurated macrocycles **22a**−**d** during the RCM reaction should not be disregarded in a total synthesis, we explored a different route toward key intermediate **23**.

The ruthenium-based RCM catalysts are characterized by exceptional compatibility with polar functional groups such as alcohols, acids, esters, ketones, aldehydes, and others. Problematic functionalities include thioethers,

(64) The use of acrylonitrile in cross-metathesis reactions was recently described: Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4035−4037.

(65) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291−293.

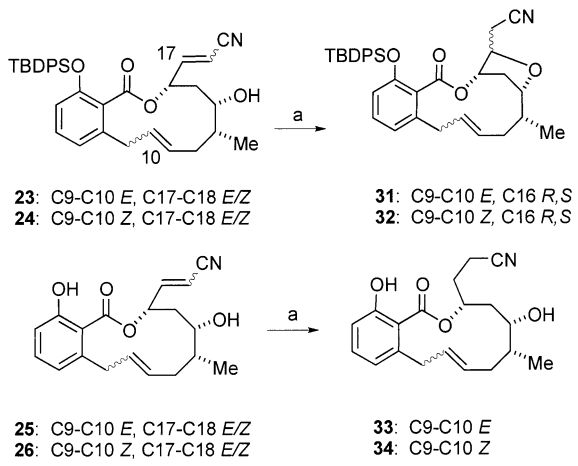
disulfides, amines, and nitriles, which are thought to be generally unsuitable for ruthenium catalysts.[48,64] Notwithstanding, we introduced the carbons C17 to C18 via a Wittig reaction applying (triphenylphosphoranyliden)-acetonitrile, anticipating that the resulting conformationally less-constrained intermediates **27** and **28,** compared to the earlier employed lactols **20**, would be appropriate precursors for the subsequent RCM reaction, although bearing a nitrile functionality. By employing the above reaction conditions, lactol **20d** (1:4 α:β mixture of diastereoisomers) gave rise to the intermediates **27** and **28** in excellent yield. Subsequent deprotection afforded the RCM-precursors **29** and **30** (Scheme 5). The following treatment of substrates **29** and **30** in CH_2Cl_2 with 10 mol % of Grubbs catalyst 1 indeed resulted in a 50% conversion after 24 h; however, the *Z*-isomer **26** was the major reaction product (20:80 ratio of **25**:**26**, entry 8, Table 1). These results are comparable to those we obtained for the corresponding conformationally restricted substrate **20a** (entry 1, Table 1) regarding the *E*:*Z* ratio, although we noted an increase in reaction time. On the basis of our earlier observations that sterically demanding substituents at the phenolic moiety enhance *E*-selectivity, we next subjected a mixture of TBDPS-protected substrates **27** and **28** to RCM reaction conditions (10 mol % of Grubbs catalyst 1). Most interestingly, the RCM reaction not only proceeded with high stereoselectivity, but also gave rise to the key intermediate **23** in excellent yield (*E*:*Z* ratio 92:8, yield 96%, entry 7, Table 1). The relatively short reaction time of 6 h for the RCM reaction indicates that the presence of the TBDPS substituent in substrates **27** and **28** not only serves as a major element of control to induce *E*-olefin geometry but also enhances the reaction rate compared to derivatives **29** and **30**, carrying a phenolic moiety.

It should be noted that the reactions of substrates **27**, **28**, **29**, and **30** under RCM conditions are some of the first examples of substrates bearing a nitrile functionality being successfully used in a RCM reaction.[48,64]

The selective reduction of the exocyclic double bond at C16 in substrates **25** and **26** was accomplished by utilizing triphenylphosphine copper hydride hexamer[65] in benzene leading to the diastereomers **33** and **34** in high yields (Scheme 6), which could be separated by column chromatography. Employing NaTeH as reducing agent also furnished the desired products;[66] however, yields in this case were significantly lower and the reaction time was 2 days. Surprisingly, the reduction of the TBDPS-protected macrocycles **23** and **24** under similar reaction conditions solely afforded the intramolecular Michael addition products **31** and **32**.

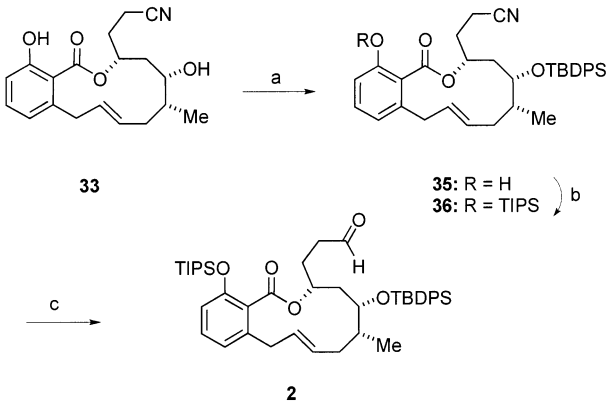
Having the macrocyclic intermediate **33** in hand, our next objective was the introduction of the identical protecting groups at positions C3 and C13 of the macrocycle, which were employed by the Labrecque group[23] in their total synthesis. We therefore selectively protected the hydroxyl group at C13 in **33** by conversion to its TBDPS-ether at elevated temperatures, followed by formation of the aromatic TIPS-ether, giving rise to **35** in moderate yield (Scheme 7). Reduction of the nitrile with DIBAL-H afforded the corresponding aldehyde **2**, completing the formal synthesis of the (+)-salicylihalamides A and B.[67]

SCHEME 6[a]



[a] Reagents and conditions: (a) $[Ph_3PCuH]_6$, benzene, rt, **31/32** (15 min, 81%), **33/34** (30 min, 94%).

SCHEME 7[a]



[a] Reagents and conditions: (a) TBDPSCl, imidazole, DMAP, DMF, 100 °C, 1 d, 84% (64% conversion). (b) TIPSOTf, 2,6-lutidine, DMF, 80 °C, 12 h, 91%. (c) DIBAL-H, toluene, −78 °C, 2.5 h, 76%.

Conclusion

A high-yielding formal total synthesis of the (+)-salicylihalamides has been achieved, employing as key synthetic strategies a chiral pool approach for the preparation of the chiral building block, and the ring-closing metathesis reaction for the formation of the macrocyclic structure. Starting from known, glucose-derived alcohol **9**, a 13-step protocol was devised that provided target aldehyde **2** in 26% overall yield. It was found that the RCM reactions had a bias toward the formation of *Z*-olefins; however, the introduction of phenolic substituents provided *E*-isomers preferentially and enhanced the rates of the reactions. Other key steps in the synthetic

(66) Zeng, P.; Hu, Y.; Hu, H. *Synth. Commun.* **1997**, *27*, 939−944.

(67) The NMR data for aldehyde **2** were identical with those of Labrecque et al.[23] We gratefully acknowledge Labrecque et al. for providing supporting NMR data.

(68) Blackman, B.; Mossman, C. J.; Yang, K. L.; Flaherty, P. T.; Georg, G. I. *Abstracts of Papers*; 219th National Meeting of the American Chemical Society, San Francisco, CA, 2000; American Chemical Society: Washington, DC, 2000; ORG 808.

sequence are a very efficient carbon−carbon bond-forming reaction with complete inversion of stereochemistry of triflate **9** with a higher order cuprate to introduce an allyl group, and the introduction of the aromatic moiety by a Mitsunobu reaction at the C2 position of a five-membered lactone. An example is provided, demonstrating that the nitrile group can be added to the functional groups that are stable under RCM conditions. An experimental procedure for a reliable large-scale synthesis of 2-allyl-6-methoxybenzoic acid (**14**) is provided also. The application of this chemistry for the synthesis of the (−)-salicylihalamides and related analogues is under study.

Experimental Section

(1′*R*,2*R*,3*R*,5*S*)-2,2-Dimethyl-5-(1′-methylbut-3′-enyl)-tetrahydrofuro[2,3-*d*][1,3]dioxole (10). To a solution of alcohol **9** (400 mg, 2.13 mmol, 1.0 equiv) and 2,6-lutidine (0.3 mL, 2.55 mmol, 1.2 equiv) in dry CH_2Cl_2 (15 mL) was added neat Tf_2O (0.4 mL, 2.34 mmol, 1.1 equiv) dropwise at 0 °C. After completion of the reaction (monitored by TLC) the mixture was quenched with water (1 mL) and extracted with Et_2O. The combined organic layers were successively washed with 1 N HCl (1.5 mL), 10% $NaHCO_3$ solution (2 mL), and brine, and dried over Na_2SO_4. The solvent was removed in vacuo at room temperature providing the crude triflate, which was kept under vacuum at −78 °C until usage. To a suspension of thoroughly dried CuCN (273 mg, 3.2 mmol, 1.5 equiv) in THF (3 mL) was added a solution of MeLi in Et_2O (1.4 M, 4.56 mL, 6.39 mmol, 3.0 equiv) dropwise at −78 °C and the solution was slowly warmed to 0 °C upon which the reaction mixture increasingly turned into a greenish solution. After addition of neat allyltributyltin (1.98 mL, 6.39 mmol, 3.0 equiv), the reaction mixture was stirred for an additional 30 min at 0 °C and then carefully cooled to −78 °C. At this point, the crude triflate was diluted with dry THF and slowly added to the reaction mixture. After 30 min, the reaction was carefully quenched by the dropwise addition of an NH_4OH solution, which had been saturated with NH_4Cl prior to use, slowly warmed to room temperature, stirred overnight, and then extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (hexane/EtOAc = 9/1) furnished 375 mg (84%) of **10**: R_f 0.74 (hexane/EtOAc = 7/3); ^{1}H NMR (400 MHz) δ 5.83−5.73 (m, 2 H), 5.05−4.99 (m, 2 H), 4.71 (t, J = 4.4 Hz, 1 H), 3.97 (ddd, J = 4.2, 7.8, 10.1 Hz, 1 H), 2.42−2.36 (m, 1 H), 2.04 (dd, J = 4.1, 13.3 Hz, 1 H), 1.91 (dt, J = 8.1, 13.8 Hz, 1 H), 1.72−1.66 (m, 1 H), 1.50 (s, 3 H), 1.53−1.45 (m, 1 H), 1.31 (s, 3 H), 0.85 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz) δ 136.9, 116.4, 110.9, 105.4, 81.8, 80.6, 38.3, 37.2, 36.7, 26.9, 26.4, 15.0; MS (ES+) m/z 230.2 HRMS (ES+) m/z calcd for $C_{12}H_{24}N_1O_3$ (M + NH_4) 230.1756, found 230.1751; IR (neat) ν_{max} 1380, 1371, 1022 cm^{-1}; $[\alpha]^{25}_D$ −22.6 (c 2.20, $CHCl_3$).

(1′*R*,2*R*,3*R*,5*S*)- and (1′*R*,2*S*,3*R*,5*S*)-5-(1′-Methylbut-3′-enyl)tetrahydrofuran-2,3-diol (11). Acetonide **10** (1.6 g, 6.21 mmol) was suspended in 70% aqueous AcOH (100 mL) and the mixture was stirred at 50 °C for 5 h. The crude reaction mixture was carefully concentrated in vacuo below 40 °C (to avoid acetate formation). Purification by silica gel column chromatograpy (hexane/EtOAc = 1/3) afforded 871 mg (83%) of **11** (ratio of α- and β-anomers 1.4:1) as a colorless solid: R_f 0.2 (hexane/EtOAc = 1/1); mp 47 °C; ^{1}H NMR (500 MHz) δ 5.82−5.72 (m, 1 H), 5.34 (d, J = 2.9 Hz, 0.58 H), 5.26 (s, 0.42 H), 5.08−4.99 (m, 2 H), 4.67 (br s, 0.58 H), 4.24−4.20 (m, 1 H), 4.14−4.07 (m, 1 H), 3.99 (br s, 0.42 H), 3.26 (br s, 0.58 H), 3.03 (br s, 0.42 H), 2.40−2.36 (m, 0.42 H), 2.30−2.25 (m, 0.58 H), 1.96−1.83 (m, 3 H), 1.74−1.59 (m, 1 H), 0.84 (d, J = 5.4 Hz, 0.42 H), 0.82 (d, J = 5.4 Hz, 0.58 H); ^{13}C NMR (125 MHz) δ 136.82, 136.79, 116.32, 116.30, 102.5, 96.9, 83.8, 80.7, 76.6, 71.9, 39.2, 38.1, 37.7, 37.6, 35.6, 35.2, 14.9, 14.6; MS (CI) m/z 172; HRMS (FAB+) m/z calcd for $C_9H_{12}O_3$ (M + H)$^+$ 173.1178, found 173.1181; IR (neat) ν_{max} 3375, 1025 cm^{-1}; $[\alpha]^{25}_D$ −6.05 (c 0.380, $CHCl_3$).

(1′*R*,3*R*,5*S*)-3-Hydroxy-5-(1′-methylbut-3′-enyl)dihydrofuran-2-one (13). A suspension of hemiacetal **11** (610 mg, 3.54 mmol, 1.0 equiv) and Ag_2CO_3/Celite (6 g, 10.63 mmol, 3 equiv) in dry benzene (30 mL) was refluxed for 1 h. After completion of the reaction, indicated by TLC and a color change from dark green to black, the reaction mixture was filtered through a short pad of silica, and the filtrate was concentrated in vacuo to give rise to 570 mg (95%) of **13** after column chromatography (hexane/EtOAc = 1/1): R_f 0.57 (hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz) δ 5.77−5.67 (m, 1 H), 5.05 (d, J = 5.9 Hz, 1 H), 5.02 (br s, 1 H), 4.50−4.42 (m, 2 H), 4.17 (s, 1 H), 2.31−2.20 (m, 3 H), 1.98−1.93 (m, 1 H), 1.81−1.74 (m, 1 H), 0.87 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz) δ 178.0, 135.4, 117.4, 82.5, 67.8, 37.4, 37.0, 33.2, 14.2; MS (EI) m/z 171; HRMS (FAB+) m/z calcd for $C_9H_{15}O_3$ 171.1021, found 171.1021; IR (neat) ν_{max} 3425, 1775, 1186, 1114 cm^{-1}; $[\alpha]^{25}_D$ +73.3 (c 3.41, $CHCl_3$).

2-Allyl-6-methoxybenzoic Acid (14). A 1-L three-neck round-bottom flask, equipped with a digital thermometer, a mechanical stirrer, and a dropping funnel, was charged with TMEDA (40 mL, 0.26 mmol, 2.2 equiv) and dry THF (100 mL), flushed with argon, and cooled to −90 °C with 2-propanol/liquid N_2. To this solution was added *sec*-BuLi (186 mL, 260 mmol, 1.4 M in cyclohexane, 2.2 equiv) slowly, maintaining the temperature below −90 °C. The resulting pale yellow solution was stirred for an additional 30 min followed by the dropwise addition of a solution of 2-methoxybenzoic acid **7** (18 g, 120 mmol, 1.0 equiv) in dry THF (55 mL) over 30 min, maintaining the internal temperature at −90 °C. The reaction mixture was stirred further, while warming to −78 °C until an orange colored and nearly clear solution was obtained (approximately 1 h). After addition of allyl bromide (40 mL, 470 mmol, 4.1 equiv) over 1 h, maintaining the temperature at −78 °C, the resulting mixture was stirred for another 30 min and then quenched slowly with water (100 mL) and warmed to room temperature. After the layers were separated, the aqueous layer was washed twice with Et_2O (100 mL), and then the organic layers were discarded. The aqueous layer was acidified with 6 N HCl (150 mL) and extracted with CH_2Cl_2 (3 L). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to provide **14** (10.5 g, 46%) as colorless crystals after column chromatography (hexane/EtOAc = 6/4): R_f 0.54 (hexane/EtOAc = 1/1); mp 91 °C; ^{1}H NMR (400 MHz) δ 7.36 (t, J = 8.0 Hz, 1 H), 6.93 (d, J = 8.0 Hz, 1 H), 6.87 (d, J = 8.0 Hz, 1 H), 5.98 (m, 2 H), 5.12 (m, 2 H), 3.91 (s, 3 H), 3.56 (d, J = 6.7 Hz, 1 H); ^{13}C NMR (100 MHz) δ 173.6, 157.2, 139.9, 136.6, 122.6, 122.4, 116.8, 109.6, 56.5, 38.3; HRMS m/z calcd for $C_{11}H_{12}O_3$ (M + H)$^+$ 193.0865, found 193.0858; IR (KBr) ν_{max} 2500−3500, 1693, 1588, 1467, 1273, 1081, 923, 775 cm^{-1}.

2-Allyl-6-hydroxybenzoic Acid (5). To a solution of benzoic acid derivative **14** (2.3 g, 12 mmol, 1.0 equiv) and *n*-Bu_4NI (5.3 g, 14 mmol, 1.2 equiv) in dry CH_2Cl_2 (100 mL) was added a solution of BCl_3 in CH_2Cl_2 (1 M, 15 mL, 1.25 equiv) dropwise over a period of 20 min at −78 °C. The reaction mixture was slowly warmed to room temperature, stirred for additional 2 h, and then quenched with water. The organic layer was separated and concentrated in vacuo to a remaining volume of about 10 mL. After addition of 6 N HCl (100 mL) the mixture was extracted three times with Et_2O. The organic layers were combined, washed with saturated $Na_2S_2O_3$ solution and brine, dried over Na_2SO_4, filtered, and finally concentrated in vacuo to yield **5** (1.9 g, 90%) as colorless crystals after recrystallization from hexane: R_f 0.55 (hexane/EtOAc = 1/1); mp 103−104 °C; ^{1}H NMR (400 MHz) δ 10.9 (s, 1 H), 7.43 (dd, J = 7.7, 8.2 Hz, 1 H), 6.95 (dd, J = 0.3, 8.0 Hz, 1 H), 6.84 (d, J = 7.7 Hz, 1 H), 6.07 (m, 2 H), 5.08 (m, 2 H), 3.81 (d, J = 6.2 Hz, 1 H); ^{13}C NMR (100 MHz) δ 176.5, 164.0, 144.9, 137.7, 136.2, 123.2, 116.9, 116.2, 110.9, 40.6; HRMS m/z calcd for $C_{10}H_{10}O_3$ (M + H)$^+$ 179.0708, found 179.0697; IR (KBr) ν_{max} 3420, 1640, 1605, 1427, 1020, 915, 760 cm^{-1}.

(1′*R*,3*S*,5*S*)-2-Allyl-6-hydroxybenzoic Acid 5-(1′-Methylbut-3′-enyl)-2-oxo-tetrahydrofuran-3-yl Ester (18a). Diethyl azodicarboxylate (1.75 mL, 11.1 mmol, 2.1 equiv) was added to a stirred solution of triphenylphosphine (2.9 g, 11.1 mmol, 2.1 equiv) in dry THF (30 mL) at −78 °C. To the resulting reaction mixture was added dropwise a solution of benzoic acid derivative **5** (1.0 g, 5.61 mmol, 1.1 equiv) in THF (20 mL), followed by the subsequent addition of a solution of lactone **13** (0.90 g, 5.29 mmol, 1.0 equiv) in THF (20 mL) at −20 °C. The reaction mixture was stirred for an additional 5 h, warmed to room temperature, and concentrated in vacuo. Column chromatography (hexane/EtOAc = 85/15) provided 1.1 g (90%) of **18a**: R_f 0.54 (hexane/EtOAc = 10/3); ^{1}H NMR (400 MHz) δ 10.65 (s, 1 H), 7.38 (t, J = 8.0 Hz, 1 H), 6.91 (d, J = 8.4 Hz, 1 H), 6.79 (d, J = 7.3 Hz, 1 H), 6.00 (m, 1 H), 5.78 (m, 1 H), 5.75 (dd, J = 10.2, 12.6 Hz, 1 H), 5.13 (d, J = 6.0 Hz, 1 H), 5.09 (s, 1 H), 5.03 (dd, J = 1.5, 10.2 Hz, 1 H), 4.94 (dd, J = 1.7, 17.2 Hz, 1 H), 4.33 (m, 1 H), 3.82 (dd, J = 6.2, 15.8 Hz, 1 H), 3.66 (dd, J = 5.8, 15.8 Hz, 1 H), 2.87 (m, 1 H), 2.39 (m, 1 H), 2.07 (m, 2 H), 1.96 (m, 1 H), 0.95 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz) δ 171.7, 170.0, 162.9, 143.4, 137.8, 135.4, 135.2, 123.1, 117.7, 116.5, 115.7, 111.5, 80.3, 70.1, 40.3, 37.7, 37.0, 32.8, 13.7; HRMS m/z calcd for $C_{19}H_{22}O_5$ $(M + H)^+$ 331.1545, found 331.1515; IR (KBr) ν_{max} 3422, 3082, 2951, 2864, 1798, 1750, 1457, 1210, 1123, 1055, 1022, 915 cm^{-1}; $[\alpha]^{25}_D$ +52.5 (c 1.00, $CHCl_3$).

(1′*R*,3*S*,5*S*)-2-Allyl-6-(*tert*-butyldiphenylsilanyloxy)-benzoic Acid 5-(1′-Methylbut-3′-enyl)-2-oxo-tetrahydrofuran-3-yl Ester (18d). A solution of phenol **18a** (1.54 g, 4.7 mmol, 1.0 equiv), *tert*-butylchlorodiphenylsilane (1.45 mL, 5.6 mmol, 1.2 equiv), imidazole (0.41 g, 6.06 mmol, 1.3 equiv), and DMAP (catalytic amount) in DMF (15 mL) was stirred at ambient temperature for 5 h. The reaction mixture was quenched with water (50 mL) and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (hexane/EtOAc = 4/1) furnished 2.6 g (98%) of **18d**: R_f 0.53 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz) δ 7.77−7.72 (m, 4 H), 7.49−7.37 (m, 6 H), 6.90 (t, J = 7.9 Hz, 1 H), 6.77 (d, J = 7.6 Hz, 1 H), 6.30 (d, J = 8.2 Hz, 1 H), 5.98 (dddd, J = 6.65, 6.62, 10.1, 16.9 Hz, 1 H), 5.83−5.73 (m, 2 H), 5.15−5.08 (m, 4 H), 4.29 (ddd, J = 5.3, 7.7, 10.6 Hz, 1 H), 3.52 (dddd, J = 6.4, 6.8, 7.7, 10.1 Hz, 2 H), 2.77 (ddd, J = 5.3, 8.6, 13.9 Hz, 1 H), 2.40−2.34 (m, 1 H), 2.13 (m, 2 H), 1.96−1.91 (m, 1 H), 1.08 (s, 9 H), 0.91 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz) δ 172.0, 167.3, 152.5, 139.3, 136.6, 135.7, 135.4, 135.0, 132.5, 132.0, 130.5, 130.34, 130.28, 129.9, 124.4, 122.1, 117.7, 117.1, 116.7, 80.0, 69.6, 37.7, 37.1, 32.9, 29.9, 26.8, 19.6, 13.7; MS (CI) m/z 586 (+NH_4); HRMS (ES+) m/z calcd for $C_{35}H_{41}NO_5Si$ $(M + NH_4)$ 586.2989, found 586.3012; IR (neat) ν_{max} 1796, 1738, 1469, 1098 cm^{-1}; $[\alpha]^{25}_D$ −77.8 (c 0.450, $CHCl_3$).

(1′*R*,2*R*,3*S*,5*S*)- and (1′*R*,2*S*,3*S*,5*S*)-2-Allyl-6-hydroxybenzoic Acid 2-Hydroxy-5-(1′-methylbut-3′-enyl)tetrahydrofuran-3-yl Ester (20a). To a solution of lactone **18a** (39 mg, 0.12 mmol, 1.0 equiv) in dry Et_2O (3 mL) was added a solution of DIBAL-H (1 M in toluene, 0.26 mL, 0.26 mmol, 2.2 equiv) dropwise at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, quenched with Rochelle solution (1 mL), and warmed to room temperature. After dilution with Et_2O (30 mL), the solution was stirred overnight after which the layers were separated. The organic layer was washed with Rochelle solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (hexane/EtOAc = 85/15) provided 32 mg (82%) of **20a** as a 1:3 mixture of α- and β-anomers: R_f 0.38 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz) δ 7.39−7.31 (m, 1 H), 6.92−6.86 (m, 1 H), 6.78−6.76 (m, 1 H), 6.10−5.92 (m, 1 H), 5.84−5.73 (m, 1 H), 5.61−5.55 (m, 0.67 H), 5.39−5.36 (m, 0.66 H), 5.08−4.93 (m, 4 H), 4.21−4.12 (m, 1 H), 3.78−3.70 (m, 2 H), 2.66−2.58 (m, 0.63 H), 2.46−2.34 (m, 1.14 H), 1.84−1.79 (m, 1.60 H), 1.28−1.19 (m, 0.63 H), 0.93−0.89 (m, 3 H).

(1′*R*,2*R*,3*S*,5*S*)- and (1′*R*,2*S*,3*S*,5*S*)-2-Allyl-6-(*tert*-butyldiphenylsilanyloxy)benzoic Acid 2-Hydroxy-5-(1′-methylbut-3′-enyl)tetrahydrofuran-3-yl Ester (20d). Following the procedure for the synthesis of **20a**, employing lactone **18d** (0.7 g, 1.2 mmol, 1.0 equiv) with DIBAL-H (1.0 M in Et_2O, 1.3 mL, 1.3 mmol, 1.1 equiv), afforded **20d** (630 mg, 90%) as a 1:4 mixture of α- and β-anomers after column chromatography (hexane/EtOAc = 4/1): R_f 0.50 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz) δ 7.77 (m, 4 H), 7.44 (m, 6 H), 6.89 (t, J = 8.0 Hz, 1 H), 6.76 (d, J = 7.6 Hz, 1 H), 6.32 (d, J = 8.2 Hz, 1 H), 5.97 (m, 1 H), 5.79 (m, 1 H), 5.62 (s, 0.8 H), 5.57 (d, J = 3.7 Hz, 0.2 H), 5.37 (dd, J = 3.1, 7.1 Hz, 0.8 H), 5.28 (m, 0.2 H), 5.08 (m, 4 H), 4.16 (q, J = 7.5 Hz, 0.8 H), 3.84 (m, 0.2 H), 3.46 (d, J = 6.4 Hz, 0.4 H), 3.40 (d, J = 6.5 Hz, 1.6 H), 3.00 (br s, 0.2 H), 2.89 (br s, 0.8 H), 2.60 (m, 1 H), 2.39 (m, 1 H), 1.96 (m, 1 H), 1.80 (m, 2 H), 1.09 (s, 9 H), 0.88 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz) δ 168.2, 167.9, 152.5, 138.8, 138.5, 136.9, 136.8, 136.7, 136.4, 135.7, 135.6, 132.5, 132.3, 132.2, 130.3, 130.2, 130.1, 128.1, 125.6, 125.4, 122.0, 121.9, 117.2, 117.1, 116.8, 116.6, 116.5, 101.0, 94.6, 82.2, 80.5, 80.3, 74.7, 39.4, 37.9, 37.8, 37.7, 37.6, 34.9, 33.8, 31.8, 31.6, 26.5, 22.9, 19.6, 15.1, 14.9, 14.4; HRMS m/z calcd for $C_{35}H_{42}O_5Si$ $(M + H)^+$ 571.2880, found 571.2861; IR (KBr) ν_{max} 3432, 3080, 2939, 2856, 1745, 1587, 1472, 1290, 1108, 828, 705 cm^{-1}; $[\alpha]^{25}_D$ +0.950 (c 1.90, $CHCl_3$).

(*E*)- and (*Z*)-(1*S*,14*R*,15*S*,17*R*)-5-(*tert*-Butyldiphenylsilanyloxy)-17-hydroxy-14-methyl-2,16-dioxatricyclo-[13.2.1.0^{0,0}]octadeca-4,6,8,11-tetraen-3-one] (21d and 22d). Procedure A (entry 4, Table 1): A solution of lactol **20d** (1.8 g, 3.2 mmol) and Grubbs catalyst 1 (78 mg, 0.096 mmol, 3.0 mol %) in CH_2Cl_2 (1 L) was refluxed for 12 h, during which the addition of 3 mol % of Grubbs catalyst 1 was repeated three times. Concentration in vacuo followed by column chromatography (5% EtOAc/hexane) provided 1.3 g (75%) of a mixture of **21d** and **22d** (75:25 ratio): R_f 0.65 (hexane/EtOAc = 4/1).

21d and **22d**: ^{1}H NMR (400 MHz) δ 7.77−7.71 (m, 4 H), 7.43−7.37 (m, 6 H), 6.80−6.76 (m, 1 H), 6.68−6.65 (m, 1 H), 6.34 (d, J = 8.3 Hz, 0.28 H), 6.28 (d, J = 8.3 Hz, 0.72 H), 5.65 (s, 0.28 H), 5.61−5.51 (m, 1.78 H), 5.41−5.32 (m, 1 H), 5.06 (d, J = 6.5 Hz, 0.78 H), 5.01 (d, J = 6.4 Hz, 0.28 H), 4.44−4.36 (m, 1 H), 4.17−4.04 (m, 0.28 H), 3.57 (dd, J = 9.6 Hz, 15.9 Hz, 0.78 H), 3.28−3.23 (m, 0.78 H), 3.02−2.81 (m, 0.56 H), 2.71−2.61 (m, 2.78 H), 2.47−2.37 (m, 0.78 H), 2.15 (d, J = 13.6 Hz, 0.78 H), 2.02−2.95 (m, 1 H), 1.91−1.70 (m, 0.84 H), 1.56−1.49 (m, 0.28 H), 1.18−0.88 (m, 12 H).

(2*E*,12*E*)-, (2*Z*,12*Z*)-, (2*E*,12*Z*)-, and (2*Z*,12*E*)-(7*S*,9*S*,-10*R*)-(3-[4-(*tert*-Butyldiphenylsilanyloxy)-9-hydroxy-10-methyl-5-oxo-7,8,9,10,11,14-hexahydro-5*H*-6-oxabenzocyclododecen-7-yl]acrylonitrile (23 and 24). Method B (from 27 and 28, entry 7, Table 1): A solution of nitriles **27** and **28** (490 mg, 0.83 mmol, ratio **27**/**28** = 2.8/1) and Grubbs catalyst 1 (20 mg, 0.025 mmol, 3 mol %) in degassed CH_2Cl_2 (190 mL) was refluxed for 6 h. Additional Grubbs catalyst 1 (9 mol %) was added after 2, 3, and 4 h reaction times, respectively. Concentration in vacuo followed by column chromatography (hexane/EtOAc = 85/15) gave rise to 448 mg (96%) of the nitriles **23** and **24** (**23**/**24** = 92:8), each as a mixture of isomers (C16/C17 E/Z = 2.8/1 [salicylihalamide numbering]): R_f 0.4 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz) δ 7.79−7.72 (m, 2 H), 7.70−7.62 (m, 2 H), 7.52−7.32 (m, 6 H), 6.94−6.68 (m, 2.35 H), 6.63 (dd, J = 4.2, 16.3 Hz, 0.65 H), 6.42 (d, J = 8.3 Hz, 0.67 H), 6.38−6.23 (m, 0.54 H), 6.13 (br dd, J = 2.5, 9.0 Hz, 0.1 H), 5.97−5.95 (br m, 0.68 H), 5.68 (dd, J = 1.8, 16.3 Hz, 0.68 H), 5.63−5.37 (m, 2.15 H), 5.30 (d, J = 11.5 Hz, 0.19 H), 4.36 (br d, J = 7.8 Hz, 0.68 H), 4.18 (br s, 0.17 H), 4.10 (br d, J = 8.7 Hz, 0.16 H), 3.95−3.89 (m, 0.12 H), 3.76−3.68 (m, 0.88 H), 3.40−3.32 (m, 0.88 H), 3.10−3.06 (m, 0.12 H), 2.36−1.55 (m, 5 H), 1.04−0.86 (m, 12 H); ^{13}C NMR (100 MHz) δ 167.9, 167.7, 166.7, 166.4, 153.0, 152.9, 152.6, 152.0, 151.9, 151.7, 150.5, 139.8, 139.7, 138.9, 138.4, 135.44, 135.40, 135.24, 135.20, 132.65, 132.59, 132.2, 132.0, 131.95, 131.93, 131.7, 131.4, 131.3, 130.6, 130.4, 130.3, 130.2, 130.09, 130.07, 129.9, 129.7, 129.6, 128.7, 128.6, 128.5, 128.4, 128.1, 127.95,

127.91, 127.86, 127.83, 125.9, 125.7, 124.6, 124.4, 123.1, 122.94, 122.87, 122.7, 117.8, 117.6, 117.4, 117.2, 116.51, 116.47, 114.7, 114.4, 100.2, 100.1, 99.3, 96.1, 72.9, 72.0, 71.9, 71.3, 71.2, 70.7, 68.9, 39.9, 39.6, 38.2, 38.1, 37.9, 37.8, 37.7, 37.5, 37.3, 37.1, 36.7, 36.4, 32.5, 32.3, 32.0, 29.7, 26.6, 26.5, 26.10, 26.07, 19.8, 19.5, 19.4, 19.3, 13.0; MS (CI) *m*/*z* 566; HRMS (FAB+) *m*/*z* calcd for $C_{35}H_{40}NO_4Si$ $(M + H)^+$ 566.2727, found 566.2713; IR (neat) ν_{max} 3490, 2227, 1736, 1458, 1281, 1113, 1066, 1027, 972, 826, 786, 755 cm^{-1}; $[\alpha]^{25}_D$ −46.6 (*c* 1.27, $CHCl_3$).

(2*E*,12*E*)-, (2*Z*,12*Z*)-, (2*E*,12*Z*)-, and (2*Z*,12*E*)-(7*S*,9*S*,-10*R*)-3-(4,9-Dihydroxy-10-methyl-5-oxo-7,8,9,10,11,14-hexahydro-5*H*-6-oxabenzocyclododecen-7-yl)acrylonitrile (25 and 26). Method B (from 23 and 24): To a solution of nitriles **23** and **24** (47 mg, 0.083 mmol, 1.0 equiv, ratio **23**/**24** = 92/8, C16/17 *E*/*Z* = 2.8:1 [salicylihalamide numbering]) in dry THF (3 mL)was added a solution of TBAF in THF (1 M, 0.11 mL, 0.11 mmol, 1.3 equiv) dropwise at ambient temperature. The reaction mixture was stirred for an additional 20 min, cooled to 0 °C, quenched with saturated NH_4Cl solution (0.5 mL) and brine (1 mL), and finally diluted with Et_2O. The layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide 27 mg (99%) of the macrocycles **25** and **26** (**25**/**26** = 92/8) as mixture of isomers (C16/17 *E*/*Z* = 3/1 [salicylihalamide numbering]) after column chromatography (Et_2O/CH_2Cl_2 = 1/4): R_f 0.34 (hexane/EtOAc = 1/1); ^1H NMR (400 MHz) δ 7.40−7.31 (m, 1 H), 6.92−6.89 (m, 1 H), 6.79−6.68 (m, 1.79 H), 6.55−6.46 (m, 0.21 H), 6.11 (dd, *J* = 7.3, 10.9 Hz, 0.17 H), 6.03−5.99 (m, 0.64 H), 5.87 (dd, *J* = 7.6, 11.5 Hz, 0.05 H), 5.76 (dd, *J* = 5.5, 11.6 Hz, 0.13 H), 5.68 (dd, *J* = 1.7, 16.3 Hz, 0.63 H), 5.56−5.42 (m, 1.19 H), 5.30−5.17 (m, 1.13 H), 4.41−4.34 (m, 0.12 H), 3.95−3.87 (m, 0.37 H), 3.75−3.68 (m, 1.51 H), 3.48−3.39 (m, 0.88 H), 3.18−3.08 (m, 0.19 H), 2.73 (brs, 0.13 H), 2.51 (t, *J* = 8.1 Hz, 0.06 H), 2.39−2.24 (m, 1.17 H), 2.05−1.78 (m, 3.46 H), 1.63 (dd, *J* = 7.9, 15.2 Hz, 0.33 H), 1.54−1.47 (m, 1.07 H), 1.36−1.20 (m, 0.83 H), 0.98−0.90 (m, 3 H); ^{13}C NMR (100 MHz) δ 171.1, 170.9, 170.8, 170.3, 163.7, 162.3, 151.8, 151.1, 150.6, 150.5, 145.0, 144.7, 143.1, 142.3, 135.5, 135.4, 135.0, 134.5, 133.6, 132.7, 131.3, 127.8, 127.0, 126.2, 124.0, 123.8, 123.6, 117.0, 116.83, 116.80, 116.7, 116.4, 114.8, 114.7, 113.4, 112.1, 111.0, 110.8, 101.6, 101.2, 100.7, 100.6, 73.4, 72.9, 72.6, 70.6, 69.8, 53.9, 39.9, 39.8, 39.32, 39.26, 38.39, 38.33, 37.8, 36.0, 35.7, 35.5, 35.3, 32.2, 31.9, 31.1, 29.9, 29.4, 28.0, 20.6, 20.1, 13.9, 13.7, 13.2; MS (FAB+) *m*/*z* 328; HRMS (ES+) *m*/*z* calcd for $C_{19}H_{22}NO_4$ $(M + H)^+$ 328.1549, found 328.1544; IR (neat) ν_{max} 3396−3200, 2226, 1730, 1294, 1025 cm^{-1}; $[\alpha]^{25}_D$ −24.6 (*c* 0.875, $CHCl_3$).

(*E*)- and (*Z*)-(1*S*,3*S*,4*R*)-2-Allyl-6-(*tert*-butyldiphenylsilanyloxy)benzoic Acid 1-(2-Cyanovinyl)-3-hydroxy-4-methylhept-6-enyl Ester (27 and 28). A suspension of lactol **20d** (1:4 ratio of α:*β* anomers, 470 mg, 0.82 mmol, 1.0 equiv) and (triphenylphosphoranylidene)acetonitrile (300 mg, 0.989 mmol, 1.2 equiv) in dry toluene (8 mL) was refluxed for 1 h, during which the reaction mixture slowly turned clear. Removal of the solvent in vacuo followed by column chromatography (hexane/EtOAc = 9/1) yielded the isomeric nitriles **27** (351 mg, 72%) and **28** (123 mg, 25%): Data for mixture: MS (CI) *m*/*z* 594; HRMS (FAB+) *m*/*z* calcd for $C_{37}H_{44}NO_4Si$ $(M + H)^+$ 594.3040, found 594.3010; IR (neat) ν_{max} 3583, 2225, 1745, 1469, 1280, 1112 cm^{-1}; $[\alpha]^{25}_D$ +4.76 (*c* 0.105, $CHCl_3$).

***E*-CN 27:** R_f 0.6 (hexane/EtOAc = 4/1); ^1H NMR (400 MHz) δ 7.72 (dt, *J* = 1.2, 8.0 Hz, 4 H), 7.47−7.38 (m, 6 H), 6.91 (t, *J* = 7.9 Hz, 1 H), 6.81−6.75 (m, 2 H), 6.37 (d, *J* = 8.1 Hz, 1 H), 6.00−5.75 (m, 3 H), 5.71 (dd, *J* = 1.5, 16.4 Hz, 1 H), 5.14−5.01 (m, 4 H), 3.68−3.63 (m, 1 H), 3.38 (d, *J* = 6.2 Hz, 2 H), 3.39 (d, *J* = 4.6 Hz, 1 H), 2.26−2.21 (m, 1 H), 1.98−1.90 (m, 2 H), 1.75 (ddd, *J* = 3.5, 10.8, 14.3 Hz, 1 H), 1.69−1.62 (m, 1 H), 1.05 (s, 9 H), 0.90 (d, *J* = 6.8, 3 H); ^{13}C NMR (125 MHz) δ 168.1, 152.5, 152.0, 138.1, 136.9, 136.2, 135.6, 135.5, 132.3, 132.1, 130.47, 130.42, 130.38, 128.2, 128.1, 125.1, 122.2, 117.5, 117.0, 116.7, 101.5, 71.9, 71.1, 39.1, 38.8, 37.7, 37.1, 26.6, 19.6, 15.4; $[\alpha]^{25}_D$ −16.1 (*c* 0.700, $CHCl_3$).

***Z*-CN 28:** R_f 0.5 (hexane/EtOAc = 4/1); ^1H NMR (400 MHz) δ 7.75 (dt, *J* = 1.4, 7.9 Hz, 4 H), 7.45−7.40 (m, 6 H), 6.90 (t, *J* = 7.9 Hz, 1 H), 6.75 (d, *J* = 7.6 Hz, 1 H), 6.59 (dd, *J* = 8.4, 11.3 Hz, 1 H), 6.35 (d, *J* = 7.8 Hz, 1 H), 6.09 (dt, *J* = 3.7, 8.6 Hz, 1 H), 6.02−5.92 (m, 1 H), 5.85−7.74 (m, 1 H), 5.48 (dd, *J* = 0.9, 11.2 Hz, 1 H), 5.14−5.00 (m, 4 H), 3.71−3.66 (m, 1 H), 3.40 (d, *J* = 6.4 Hz, 2 H), 2.30−2.24 (m, 1 H), 2.13−2.05 (m, 2 H), 2.00−1.92 (m, 1 H), 1.79 (dt, *J* = 4.0, 10.4 Hz, 1 H), 1.71−1.64 (m, 1 H), 1.07 (s, 9 H), 0.90 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz) δ 167.7, 152.5, 151.8, 138.3, 137.1, 136.3, 135.5, 132.5, 132.2, 130.3, 130.2, 128.1, 122.1, 117.3, 116.9, 116.6, 100.9, 72.0, 71.2, 39.1, 38.6, 37.7, 37.0, 26.6, 19.6, 15.4; $[\alpha]^{25}_D$ +10 (*c* 0.05, $CHCl_3$).

(*E*)- and (*Z*)-(7*R*,9*S*,10*R*)-3-(4,9-Dihydroxy-10-methyl-5-oxo-7,8,9,10,11,14-hexahydro-5*H*-6-oxabenzocyclododecen-7-yl)propionitrile (33 and 34). To a suspension of diols **25** and **26** (314 mg, 0.96 mmol, 1.0 equiv, ratio 92:8) in dry benzene (5 mL) was added neat $[Ph_3PCuH]_6$ (941 mg, 0.48 mmol, 0.5 equiv) at 0 °C, and the resulting reaction mixture was stirred at this temperature until its color had turned from red to dark brown (approximately 30 min). After subsequent warming to room temperature and filtration through a short pad of silica, the resulting filtrate was concentrated in vacuo. Column chromatography (EtOAc/hexane = 1/1) gave rise to 297 mg (94%) of the nitriles **33** and **34** (**33**/**34** = 92/8). Nitrile **33**, colorless solid: R_f 0.29 (hexane/EtOAc = 1/1); mp 198−200 °C; ^1H NMR (acetone-d_6, 400 MHz) δ 9.25 (br s, 1 H), 7.19 (t, *J* = 8.1 Hz, 1 H), 6.87 (d, *J* = 8.2 Hz, 1 H), 6.74 (d, *J* = 7.5 Hz, 1 H), 5.43−5.27 (m, 3 H), 4.20−4.15 (m, 1 H), 3.70 (d, *J* = 4.6 Hz, 1 H), 3.59 (dd, *J* = 8.4, 16.3 Hz, 1 H), 3.37 (m, 1 H), 2.84−2.69 (m, 2 H), 2.31−2.27 (m, 1 H), 2.03−1.72 (m, 5 H), 1.35 (dd, *J* = 9.2, 15.2 Hz, 1 H), 0.87 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 168.4, 155.5, 140.0, 131.4, 130.7, 129.2, 122.1, 120.0, 114.6, 73.3, 70.3, 38.1, 37.9, 37.6, 37.1, 37.0, 32.5, 13.2, 13.0; MS (FAB+) *m*/*z* 330.2; HRMS (FAB+) *m*/*z* calcd for $C_{19}H_{24}N_1O_4$ $(M + H)^+$ 330.1705, found 330.1698; IR (KBr) ν_{max} 3440−3185, 2247, 1701, 1680, 1469, 1294, 1047, 778 cm^{-1}; $[\alpha]^{25}_D$ +28.7 (*c* 0.440, MeOH).

Nitrile **34**, colorless oil: R_f 0.35 (hexane/EtOAc = 1/1); ^1H NMR (acetone-d_6, 400 MHz) δ 10.7 (s, 1 H), 7.40 (t, *J* = 8.7 Hz, 1 H), 6.86 (d, *J* = 8.3 Hz, 1 H), 6.85 (d, *J* = 7.5 Hz, 1 H), 5.50 (quintet, *J* = 5.7 Hz, 1 H), 5.29 (t, *J* = 11.1 Hz, 1 H), 5.13 (t, *J* = 10.4 Hz, 1 H), 4.52 (dd, *J* = 10.2, 15.2 Hz, 1 H), 3.81−3.73 (m, 2 H), 3.08 (dq, *J* = 2.7, 15.2 Hz, 1 H), 2.62 (t, *J* = 7.4 Hz, 2 H), 2.31−2.09 (m, 4 H), 1.88−1.77 (m, 2 H), 1.58 (q, *J* = 8.0 Hz, 1 H), 0.97(d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 171.3, 162.3, 144.7, 134.7, 131.0, 128.7, 123.3, 119.7, 116.1, 113.5, 74.6, 68.9, 39.8, 35.6, 34.4, 32.2, 31.0, 13.1, 12.9.

(*E*)-(7*R*,9*S*,10*R*)-3-[9-(*tert*-Butyldiphenylsilanyloxy)-4-hydroxy-10-methyl-5-oxo-7,8,9,10,11,14-hexahydro-5*H*-6-oxabenzocyclododecen-7-yl]propionitrile (35). A solution of diol **33** (28 mg, 0.085 mmol, 1.0 equiv), imidazole (20 mg, 0.3 mmol, 3.5 equiv), DMAP (catalytic amount), and TBDPSCl (0.066 mL, 0.26 mmol, 3.05 equiv) in dry DMF (2 mL) was stirred at 100 °C for 1 day, quenched with H_2O, extracted with Et_2O, and washed with brine (2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to provide 26 mg (54%) of the phenol **35** and 10 mg of starting material (36%) after column chromatography (hexane/EtOAc/ = gradient 9/1 to 1/1): R_f 0.48 (hexane/EtOAc = 7/3); ^1H NMR (400 MHz) δ 10.8 (br s, 1 H), 7.56−7.55 (m, 4 H), 7.30−7.19 (m, 7 H), 6.82 (d, *J* = 8.3 Hz, 1 H), 6.55 (d, *J* = 7.4 Hz, 1 H), 5.25−5.22 (m, 1 H), 4.8 (br s, 2 H), 3.55−3.51 (m, 1 H), 3.47 (d, *J* = 8.4 Hz, 1 H), 3.17 (d, *J* = 16.4 Hz, 1 H), 2.35−2.20 (m, 2 H), 1.96−1.84 (m, 3 H), 1.73−1.57 (m, 3 H), 1.48 (dd, *J* = 8.3, 14.9 Hz, 1 H), 0.98 (s, 9 H), 0.90 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz) δ 170.6, 162.7, 142.9, 135.9, 135.7, 134.2, 133.9, 133.4, 132.6, 129.7, 129.5, 127.5, 127.4, 126.4, 123.3, 119.1, 116.5, 112.5, 73.4, 72.7, 39.0, 37.8, 36.9, 36.5, 31.4,

27.1, 19.2, 13.9, 13.4; HRMS (ES+) *m*/*z* calcd for $C_{35}H_{45}N_2O_4Si$ (M + NH_4) 585.3149, found 585.3129; IR (neat) ν_{max} 3243, 2247, 1687, 1454, 1214, 749 cm^{-1}; $[\alpha]^{25}_D$ +103 (*c* 0.675, $CHCl_3$).

(*E*)-(7*R*,9*S*,10*R*)-3-[9-(*tert*-Butyldiphenylsilanyloxy)-10-methyl-5-oxo-4-(triisopropylsilanyloxy)-7,8,9,10,11,14-hexahydro-5*H*-6-oxabenzocyclododecen-7-yl]propionitrile (36). To a solution of phenol **35** (91 mg, 0.16 mmol, 1.0 equiv) and 2,6-lutidine (0.024 mL, 0.21 mmol, 1.3 equiv) in dry DMF (5 mL) was added triisopropyltrifluoromethanesulfonate (0.052 mL, 0.19 mmol, 1.2 equiv) neat at 0 °C, then the mixture was warmed to room temperature and then stirred at 80 °C for 15 h. The reaction mixture was quenched with water and extracted with Et_2O (50 mL). The combined organic layers were washed with brine (3 × 2 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (5% EtOAc/hexane) provided 106 mg (91%) of the protected macrocycle **36**: R_f 0.31 (5% EtOAc/hexane); ^{1}H NMR (400 MHz) δ 7.84−7.76 (m, 4 H), 7.48−7.37 (m, 6 H), 7.10 (t, *J* = 8.0 Hz, 1 H), 6.74 (d, *J* = 8.3 Hz, 1 H), 6.69 (d, *J* = 7.5 Hz, 1 H), 5.25 (br s, 1 H), 5.13 (dd, *J* = 9.3, 15.0 Hz, 1 H), 4.62 (br s, 1 H), 4.16 (br s, 1 H), 3.39 (dd, *J* = 9.3, 16.1 Hz, 1 H), 3.18−3.13 (m, 1 H), 2.41−2.29 (m, 2 H), 1.96 (br s, 3 H), 1.72 (dd, *J* = 7.8, 15.0 Hz, 1 H), 1.60 (br s, 2 H), 1.51 (dd, *J* = 7.8, 15.0 Hz, 1 H), 1.27 (septet, *J* = 7.3 Hz, 3 H), 1.11 (s, 9 H), 1.10 (d, *J* = 7.6 Hz, 6 H), 1.08 (d, *J* = 8.3 Hz, 6 H), 1.06 (d, *J* = 7.4 Hz, 6 H), 0.88 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (100 MHz) δ 166.8, 152.6, 138.8, 136.1, 136.0, 134.1, 133.8, 129.3, 129.26, 128.1, 127.2, 127.17, 126.2, 122.5, 119.2, 116.6, 73.3, 71.3, 37.3, 35.9, 31.8, 27.0, 19.2, 17.7, 17.68, 17.5, 12.8, 12.7; MS (FAB+) *m*/*z* 724.6; HRMS (ES+) *m*/*z* calcd for $C_{44}H_{62}NO_4Si_2$ (M + H)$^+$ 724.4217, found 724.4235; IR (neat) ν_{max} 2254, 1738, 1461, 1119, 1061, 770 cm^{-1}; $[\alpha]^{25}_D$ +1.23 (*c* 1.39, $CHCl_3$).

(*E*)-(7*R*,9*S*,10*R*)-3-[9-(*tert*-Butyldiphenylsilanyloxy)-10-methyl-5-oxo-4-(triisopropylsilanyloxy)-7,8,9,10,11,14-hexahydro-5*H*-6-oxabenzocyclododecen-7-yl]propionaldehyde (2). To a solution of **36** (21 mg, 0.03 mmol, 1.0 equiv) in dry toluene (2.3 mL) was added a solution of DIBAL-H (1 M in toluene, 0.039 mL, 0.039 mmol, 1.3 equiv) dropwise at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, quenched with Rochelle solution (1 mL), warmed to room temperature, and stirred for an additional 2 h. After extracting the reaction mixture three times with Et_2O, the combined organic layers were washed with Rochelle solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (5% EtOAc/hexane) provided 16 mg (76%) of **2**: R_f 0.31 (hexane/EtOAc = 19/1); ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.67 (s, 1 H), 7.79−7.77 (m, 2 H), 7.69−7.67 (m, 2 H), 7.38−7.30 (m, 6 H), 7.05 (t, *J* = 8.0 Hz, 1 H), 6.71 (d, *J* = 8.2 Hz, 1 H), 6.63 (d, *J* = 7.5 Hz, 1 H), 5.3 (br s, 1 H), 5.02−4.96 (m, 1 H), 4.39 (br s, 1 H), 4.16 (d, *J* = 7.4 Hz, 1 H), 3.27−3.19 (m, 1 H), 3.07−3.03 (m, 1 H), 2.50 (t, *J* = 7.6 Hz, 2 H), 1.89−1.77 (m, 3 H), 1.64 (dd, *J* = 8.5, 15.4 Hz, 1 H), 1.53−1.45 (m, 3 H), 1.29−1.11 (m, 3 H), 0.99−0.93 (m, 27 H), 0.75 (d, *J* = 5.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.3, 167.2, 152.8, 139.0, 136.4, 136.3, 134.3, 134.28, 129.45, 129.42, 129.3, 128.3, 127.4, 127.3, 126.9, 125.5, 122.6, 116.8, 73.6, 72.5, 39.5, 37.5, 36.2, 30.3, 29.7, 28.2, 27.2, 19.5, 17.95, 17.92, 14.1, 13.0; HRMS (ES+) *m*/*z* calcd for $C_{44}H_{63}O_5Si_2$ (M + H)$^+$ 727.4214, found 727.4201; IR (neat) ν_{max} 1727, 1461, 1285, 1112, 1064, 739 cm^{-1}; $[\alpha]^{25}_D$ −1.50 (*c* 0.740, $CHCl_3$).

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Supporting Information Available: Experimental procedures and spectral data for compounds **12**, **16**, **17**, **18b**, **18c**, **20b**, **20c**, **21a/22a**, **21b/22b**, **21c/22c**, **25/26** (method A from **29/30**), **21d/22d** (procedure B: entry 6, Table 1), **23/24** (method A) from **21d**/**22d**, **29/30**, and **31/32** and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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