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Toward the Synthesis of Norzoanthamine: Complete Fragment Assembly

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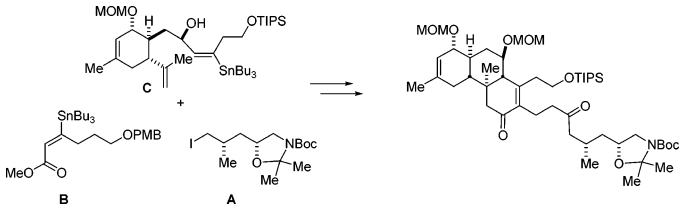

The complex marine alkaloid norzoanthamine (**2**) was envisioned to be assembled from three key building blocks: the C_1-C_5 fragment **A**, the C_6-C_{10} fragment **B**, and the $C_{11}-C_{24}$ fragment **C**. The synthesis of fragment **A** was achieved in 14 steps and 33% overall yield from (*R*)-γ-hydroxymethyl-γ-butyrolactone. Fragment **B** was made in two steps from PMB-protected 4-pentynol in 76% yield. The $C_{11}-C_{24}$ fragment **C** was made from (*S*)-carvone via (*R*)-isocarvone in 18 steps (6% overall yield). The convergent stereoselective synthesis of the entire carbon framework (C_1-C_{24}) of the target molecule was achieved via the following assemblage. Alkenyl iodide **20** derived from the $C_{11}-C_{24}$ fragment **C** was coupled to fragment **B** (C_6-C_{10}) through a high-yielding Stille coupling reaction of these two sterically very demanding coupling partners, affording the key Diels−Alder precursor **24**. The intramolecular Diels−Alder reaction proceeded smoothly in excellent yield and diastereoselectivity, generating the tricyclic trans-anti-trans perhydrophenanthrene motif of norzoanthamine (C_6-C_{24}). The final fragment coupling between lithiated fragment **A** (C_1-C_5) and aldehyde **40** (C_6-C_{24}) has also been successfully accomplished affording the entire carbon framework of the natural product.

Introduction

As part of a program to study toxic marine organisms in the early 1980s, the species *Zoanthus* sp. was found off the coast of Visakhapatnam, India. A novel marine alkaloid, zoanthamine **1**, was isolated, and its structure and relative configuration were established by means of X-ray crystallography and NMR spectroscopy in 1984 (Figure 1).[1] The absolute configuration remained elusive until 1997, when Uemura and co-workers published a report specifying the absolute stereostructure, based on Mosher's ester analysis of a derivative of norzoanthamine **2**.[2] The zoanthamine family is a structurally unique class of densely functionalized heptacyclic alkaloids[3] which exhibit an impressive range of biological activity. For example, norzoanthamine, as well as other family members, that is, oxyzoanthamine **3**, norzoanthaminone **4**, and epinorzoanthamine **7**, have been reported to exhibit anticancer activity by inhibition of the growth of P388 murine leukemia cells, with IC_{50} values of 24, 1.0, 2.6, and 7.0 μg/mL, respectively.[4] Furthermore, 11-hydroxyzoanthamine **5** and a synthetic derivative of norzoanthamine have shown strong inhibition against thrombin-, collagen-, and arachidonic acid-induced aggregation, while zoanthenol **6** has displayed a selective inhibitory activity induced

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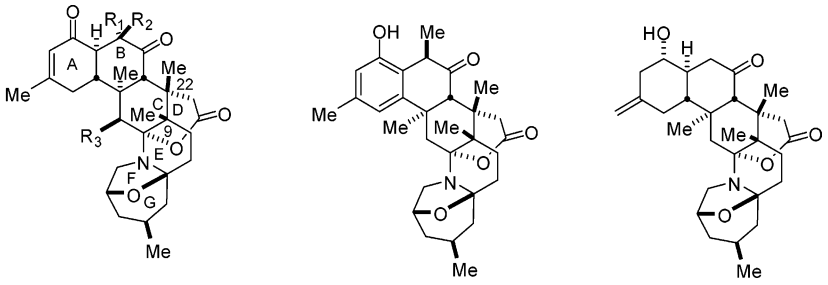

Zoanthamine **1**, R_1=H; R_2=CH_3; R_3=H
Norzoanthamine **2**, R_1=H; R_2=H; R_3=H
Oxyzoanthamine **3**, R_1=H; R_2=CH_2OH; R_3=H
Norzoanthaminone **4**, R_1=R_2=H; R_3=O
11-Hydroxyzoanthamine **5**, R_1=R_2=CH_3; R_3=OH

Zoanthenol **6**

Epinorzoanthamine **7**

FIGURE 1. Family members of the zoanthamine alkaloids.

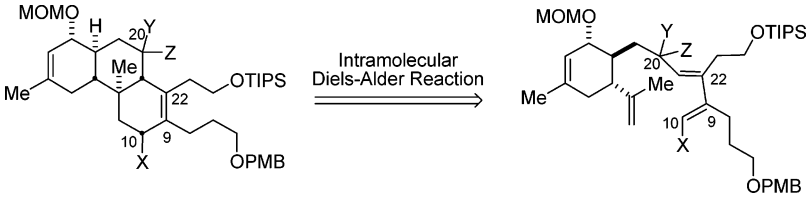

FIGURE 2. Retrosynthetic illustration of the key intramolecular Diels−Alder reaction.

by collagen, thereby rendering them viable leads as antiplatelet drugs.[5] Platelet aggregation plays a crucial role in physiological hemostasis and pathological thrombosis. A significant disease area of the latter is arterial thrombosis, which includes myocardial infarction, stroke, and other cardiovascular diseases.[5]

With their enticing structure and intriguing biological profile, the zoanthamine alkaloids have sparked considerable interest from the synthetic community. To date, as far as we are aware, six research groups other than our own have reported efforts toward the total synthesis of zoanthamine and/or congeners: Kobayashi,[6] Williams,[7] Hirama,[8] Theodorakis,[9] Irifune,[10] and Miyashita.[11] The Miyashita group is currently alone in having completed this formidable task, with the total synthesis of norzoanthamine **2**.

Results and Discussion

As shown in Figure 2, a key step in our proposed total synthesis of the zoanthamine alkaloids is an intramolecular Diels−Alder reaction. From previous synthetic efforts, which included elaborate model studies, important intelligence was gathered.[12] To ensure the success of the Diels−Alder reaction, the following are required: (1) no electron-donating (oxygen) substituent at C_{10}, but rather an electron-withdrawing group (2) alcohol and not ketone functionality at C_{20}, (3) (*R*)-configured alcohol at C_{20}, and (4) equatorial and not axial oriented MOM ether at C_{17} (Figure 3). Therefore, inspired by a model study based on carvone as a surrogate for the zoanthamine A-ring, and the other major clues collected in our previous campaign, a modified route to the zoanthamine alkaloids was designed with norzoanthamine (**2**) as the prime target. Based on the biological activity data published for the zoanthamine family in recent years, norzoanthamine seems the most promising drug lead in many disease areas.[4,5]

(−)-Isocarvone **8** was synthesized following the procedure of Theodorakis[13] and incorporating minor changes recently reported by Deslongchamps.[14] The stereoselective alkylation of the lithium enolate of (−)-isocarvone **8** with ethyl bromoacetate proceeded smoothly, providing a 9:1 diastereomeric mixture of ketoesters of which the desired trans ketoester **9** could be

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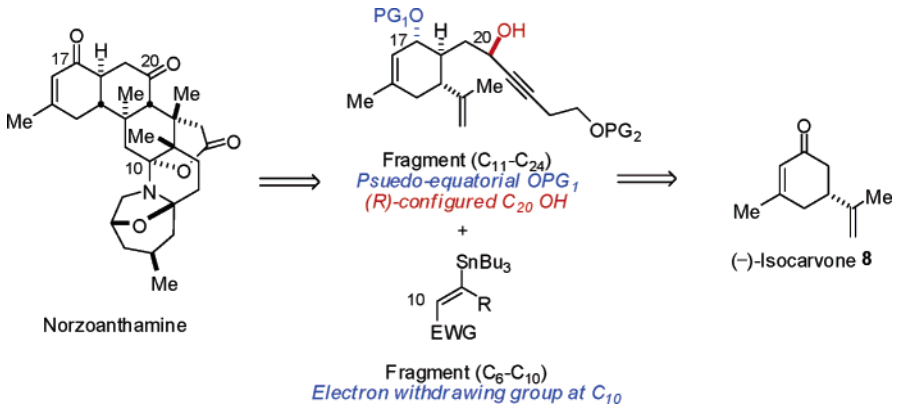
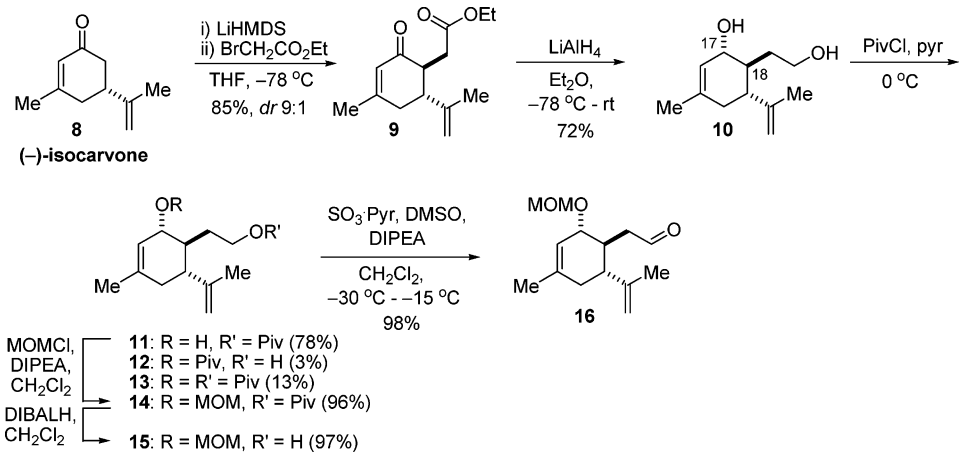
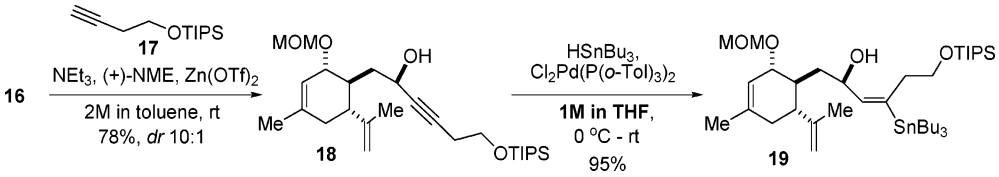


FIGURE 3. Overview of the retrosynthetic analysis of norzoanthamine.

SCHEME 1



SCHEME 2



isolated in 85% yield (Scheme 1). Diastereoselective lithium aluminum hydride reduction of ketoester **9** in diethyl ether afforded diol **10** as a crystalline solid in 72% yield. The configuration at the two new stereocenters (C_{17} and C_{18}, norzoanthamine numbering) was confirmed by X-ray crystallography, which showed the desired and expected equatorial arrangement at both sites.[15] Subsequent selective pivaloyl protection of the primary C_{20} hydroxyl group of diol **10** afforded 78% of the desired **11**. The moderate yield was due to formation of significant amounts of byproduct containing a pivaloyl group at the secondary C_{17} hydroxyl group (3% **12** and 13% **13**). Pivalate **11** was converted to the corresponding MOM ether **14** in excellent yield (96%) followed by reductive removal of the pivaloyl ester using diisobutyl aluminum hydride affording alcohol **15** in 97% yield. Oxidation of the C_{20} hydroxyl group to the corresponding aldehyde **16** was accomplished via the Parikh−Doering procedure[16] in 98% yield.

The stereoselective formation (78% yield, dr = 10:1) of propargylic alcohol **18** from aldehyde **16** and alkyne **17** proceeded smoothly using the conditions developed by Carreira and co-workers (Scheme 2).[17] In our hands, the ensuing hydrostannylation with similar substrates had previously suffered from a lack of reproducibility (running the reaction at 0.1 M concentration and syringe pump addition of the tributyltin hydride at room temperature). By increasing the concentration to 1 M and adding the tributyltin hydride at 0 °C the hydrostannylation reaction became highly reliable and vinyl stannane **19** could be obtained in an excellent 95% yield (Scheme 2).

The iodo-destannylation reaction of vinyl stannane **19** proved to be exceedingly prone to side reactions. The addition of a solution of iodine in dichloromethane to a solution of vinyl

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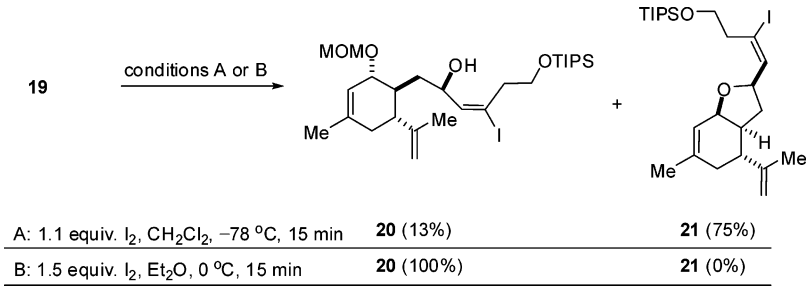
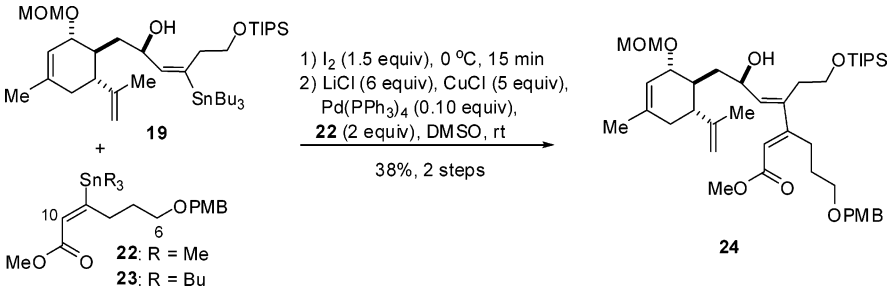
SCHEME 3



A: 1.1 equiv. I_2, CH_2Cl_2, −78 °C, 15 min	**20** (13%)	**21** (75%)
B: 1.5 equiv. I_2, Et_2O, 0 °C, 15 min	**20** (100%)	**21** (0%)

SCHEME 4

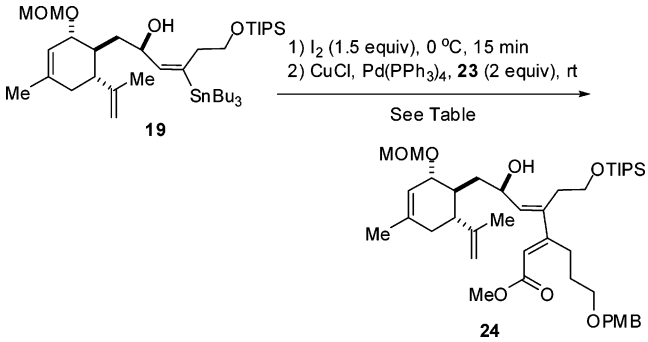


stannane **19** in dichloromethane precooled to −78 °C, resulted predominantly in formation of bicyclic ether **21** (75%) and only 13% yield of the desired vinyl iodide **20** (Scheme 3). A remarkable solvent effect was observed when switching from dichloromethane to diethyl ether. No reaction was observed between stannane **19** and iodine at −78 °C in diethyl ether, but running the reaction at 0 °C for 15 min resulted in quantitative formation of the desired iodide **20**.

The stage was now set for the first fragment coupling process (Scheme 4) which called for a Stille reaction between two sterically congested partners. On earlier occasions with similar systems, only the Corey-modified Stille reaction[18] provided the desired cross-coupling products, albeit in disappointingly low yields.[12d,e] In our initial attempts to improve the yield, the sterically less-hindered trimethyltin species **22** was used instead of the tributylstannane **23** (Scheme 4). Unfortunately, the coupling reaction provided only 38% of the desired **24** over the two-step sequence.

The fact that no byproducts derived from the $C_{11}-C_{24}$ fragment were observed and that the mass balance was off by 62% after the Stille coupling, led us to surmise that a water soluble byproduct was formed, which was removed during alkaline aqueous workup. One possibility could be that the Corey conditions (excess lithium chloride and copper chloride in DMSO) used in the Stille reaction were not only promoting the coupling reaction, but also inducing cleavage of the methyl ester in **22** and **24**, similar to the first step in the Krapcho reaction.[19] The carboxylic acid thus formed would then be removed during aqueous alkaline (aq. ammonia) workup, explaining the poor mass balance of the reaction. Another point of concern was the homocoupling of stannane **22**, which complicated chromatographic purification owing to coelution with coupling product **24**. On the basis of the hypothesis that lithium chloride in DMSO was hydrolyzing the ester moiety, the reaction was performed in DMSO omitting lithium chloride

TABLE 1



entry	solvent	equiv $Pd(PPh_3)_4$	equiv CuCl	time [h]	yield [%]
1	DMSO	0.1	1	6	61
2	DMSO/THF (1:1)	0.1	1	12	66
3	THF	0.1	1	50	48
4	MeCN	0.1	1	49	51
5	DMA	0.1	1	6	70
6	NMP	0.1	1	5	71
7	**NMP/THF (1:1)**	**0.1**	**1**	**10**	**74**
8	NMP/THF (1:9)	0.1	1	48	62
9	**NMP/THF (1:1)**	**0.1 + 0.045**	**1 + 0.25**	**10**	**82**[a]

[a] Additional $Pd(PPh_3)_4$ (0.045 equiv) was added in three portions during the reaction, and additional CuCl (0.25 equiv) was added once during the reaction.

entirely, while only 1 equiv of copper chloride was used. Furthermore, tributylstannane **23** was used instead of trimethyl stannane **22**. A marked improvement was observed, affording coupling product **24** in 61% yield, (Table 1, entry 1). Subsequently, different solvents and combinations of solvents were screened. A general observation was that the presence of THF as cosolvent decreased the amount of stannane homocoupling product, but on the other hand resulted in longer reaction times (Table 1, entries 2, 7, 8, and 9). Running the reaction in only THF or MeCN resulted in reaction times above 2 days, providing only modest yields of 48% and 51%, respectively (Table 1, entry 3 and 4). Using DMA or NMP gave comparably good results with yields around 70%, although the reaction in

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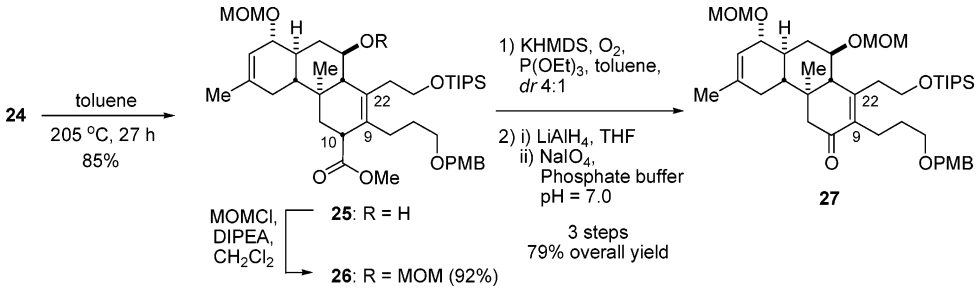
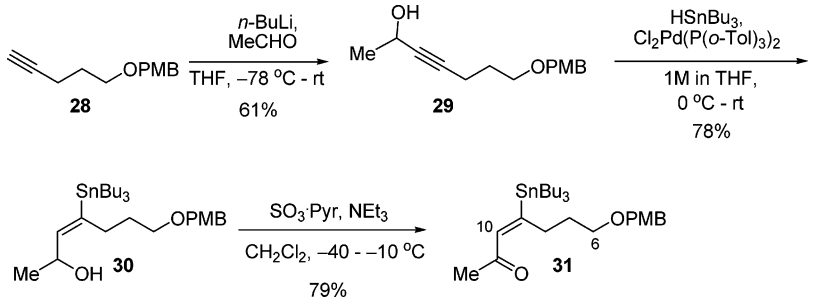
SCHEME 5



SCHEME 6



NMP was somewhat faster (Table 1, entry 5 and 6). Combining NMP with THF in a 1:1 ratio provided the best isolated yield of coupling product **24** (74% yield, Table 1, entry 7). Using a NMP/THF solvent ratio of 1:9 did not provide any improvement to the reaction. Inspired by a report from Tadano and coworkers,[20] we added several portions of tetrakistriphenylphosphine palladium(0) and copper chloride during the reaction and pleasingly 82% yield of the desired coupling product could then be isolated (Table 1, entry 9).

The key intramolecular Diels−Alder (IMDA) reaction was now at hand and worked admirably, providing cycloadduct **25** in 85% yield, after heating **24** in toluene for 27 h at 205 °C in a sealed Carius tube (Scheme 5). A crucial observation here was that precursor **24** should be completely free of even trace amounts of residual Bu_3SnI from the Stille coupling to obtain reliable results in the IMDA reaction. The free hydroxyl group at C_{20} in cycloadduct **25** was converted into the corresponding MOM ether **26** under standard conditions in 92% yield (Scheme 5).

The next task involved finding conditions to successfully perform the crucial oxidative decarboxylation at C_{10}, to access enone **27** (Scheme 5) which in turn would allow introduction of the two vicinal methyl groups at C_9 and C_{22} via an initial Michael addition. Several different procedures for oxidative decarboxylation have been reported in the literature.[21] After extensive experimentation the following three-step sequence was found to be the most favorable; α-hydroxylation, reduction, and diol cleavage. α-Hydroxylation of the potassium enolate of ester **26** using molecular oxygen provided the corresponding α-hydroxy ester in 86% yield as a 4:1 mixture of diastereomers. Subsequent reduction of the α-hydroxy ester failed using either lithium borohydride or diisobutyl aluminum hydride which resulted only in decomposition. Lithium aluminum hydride provided the desired diol, but the product was unstable, presumably because of diene formation by elimination of the allylic alcohol at C_{10}. A one-pot strategy to afford enone **27** was therefore developed, in which the α-hydroxy ester dissolved in THF was exposed to lithium aluminum hydride at −78 °C and warmed to room temperature over a period of 1 h, then cooled to 0 °C, followed by the addition of a phosphate buffer (pH = 7.00) and sodium periodate. This technique afforded enone **27** in 85% yield. Further optimization of the oxidative decarboxylation sequence was achieved by use of the crude mixture from the α-hydroxylation reaction of ester **26** in the subsequent reduction/oxidative cleavage reaction, thus providing enone **27** in 79% overall yield from ester **26**.

Simultaneously, a different strategy utilizing a Baeyer−Villiger reaction to obtain the desired oxidation state at C_{10} was explored, with a methyl ketone appendage as a precursor. In this strategy a methyl ketone was positioned at C_{10} instead of a methyl ester. The synthesis of the modified C_6−C_{10} coupling partner **31** was achieved in three steps from alkyne **28** (Scheme 6).

The subsequent three-step sequence, that is, Stille coupling, IMDA reaction, and MOM ether formation to achieve the desired Baeyer−Villiger precursor **33**, proceeded under conditions similar to those developed for the methyl ester series (Table 1 and Scheme 5). Unfortunately, the projected Baeyer−Villiger reaction performed under alkaline conditions afforded only a complex mixture of products, all of which still contained a ketone functionality based on ^{13}C NMR analysis (Scheme 7).

A di-*p*-nitrobenzoyl ester derivative achieved in two steps from the cycloadduct of **32** was prepared (**35**),[22] and a single-crystal X-ray analysis was performed, confirming the stereo-

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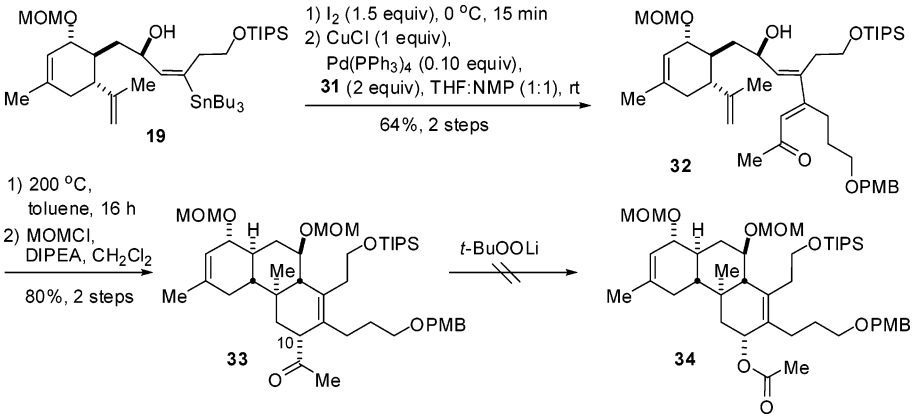
(21) For rearrangement of acyl peroxides see: (a) Kienzle, F.; Holland, G. W.; Jernow, J. L.; Kwoh, S.; Rosen, P. *J. Org. Chem.* **1973**, *38*, 3440−3442. (b) Field, S. J.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1982**, 591−593. (c) Akhtar, M.; Gani, D. *Tetrahedron* **1987**, *43*, 5341−5349. (d) Shiozaki, M.; Ishida, N.; Sato, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3950−3958. (e) Hatanaka, M.; Ueda, I. *Chem. Lett.* **1991**, 61−64. For Borodin-Hunsdiecker type oxidations see: (f) Sternbach, D. D.; Hughes, J. W.; Burdi, D. F.; Banks, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 2149−2153. (g) Patel, D. V.; Vanmiddlesworth, F.; Donaubauer, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 4603−4614. For α-hydroxylation, reduction, and diol cleavage see: (h) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. (i) Snyder, S. A.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 740−742.

SCHEME 7



chemical outcome of the IMDA reaction to be a result of an exo transition state (Figure 4).[23] The Baeyer−Villiger strategy was not further pursued, and we now concentrated solely on the route via ester **26**.

With a high-yielding and reproducible synthesis of the C_6-C_{24} fragment at hand focus was then directed toward the synthesis of the C_1-C_5 fragment (Scheme 8) as well as the final fragment assembly. The C_1-C_5 fragment was obtained from azide **36** which was available from a previously described route.[24] Cleavage of the MOM ether in azide **36** was achieved using a combination of zinc bromide and *n*-butyl thiol following a protocol developed recently by Rawal and co-workers.[25] Subsequent hydrogenation of the azide moiety using Pd/C under a hydrogen atmosphere in the presence of Boc_2O provided the corresponding carbamate. This was followed by installation of an acetonide and reductive removal of the pivaloyl ester affording alcohol **37** in 81% yield for the four-step sequence. Iodide **38** was obtained in 95% yield by subjecting alcohol **37** to a mixture of iodine, imidazole, and triphenylphosphine, thus setting the stage for the final fragment coupling process.

The C_6-C_{24} aldehyde coupling partner **40** was prepared from enone **27** starting with cleavage of the C_6 PMB ether using DDQ to afford alcohol **39** in 72% yield as a colorless oil, which solidified upon standing and could be recrystallized to provide crystals suitable for X-ray crystallographic analysis.[26] The crystal structure confirmed the (*R*)-configuration at C_{20} installed through the diastereoselective Carreira addition and the (*S*)-configuration at both C_{12} and C_{21} set by an exo selective IMDA reaction. The desired aldehyde **40** was obtained in excellent yield (90%) by oxidation of alcohol **39** via the Parikh−Doering reaction (Scheme 9).

The coupling of fragment **A** (C_1-C_5) with freshly prepared aldehyde **40** was achieved by subjecting an ethereal solution of iodide **38** to *tert*-butyl lithium at −78 °C for 4 min, followed by the addition of aldehyde **40** to provide a diastereomeric mixture of alcohols. The mixture of alcohols was immediately oxidized using the Parikh−Doering protocol to the corresponding diketone **41** in an as yet unoptimized overall yield of 25% for the two-step sequence.

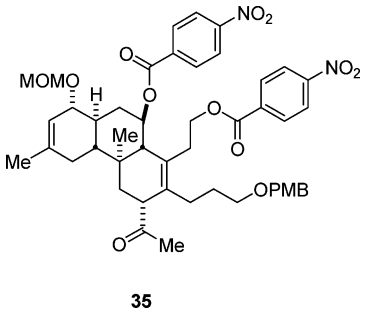
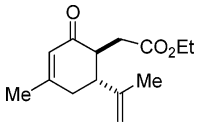


FIGURE 4. The stereochemical outcome of the IMDA reaction was verified by a X-ray crystal structure of di-*p*-nitrobenzoyl ester **35**.

In conclusion, a stereoselective synthesis of the C_1-C_{24} carbon framework of norzoanthamine **2** has been achieved. In this route, alkenyl iodide **20**, corresponding to the $C_{11}-C_{24}$ fragment of norzoanthamine, was obtained in nine steps from the known (−)-isocarvone. Coupling of **20** to the C_6-C_{10} fragment **23** through a high-yielding Stille reaction involving two sterically demanding coupling partners afforded the key Diels−Alder precursor **24**. The intramolecular Diels−Alder reaction proceeded smoothly in excellent yield and diastereoselectivity, generating the trans-anti-trans perhydrophenanthrene motif (C_6-C_{24}) of norzoanthamine, the desired stereochemistry being verified by several X-ray crystal structures. The final fragment coupling between lithiated **38** (C_1-C_5) and aldehyde **40** (C_6-C_{24}) was also accomplished, affording diketone **41** containing 27 out the 29 carbon atoms present in norzoanthamine. Current efforts are focused on the nontrivial issue of installation of the vicinal C_9 and C_{22} quartenary centers of norzoanthamine and the final advance to the target.

Experimental Section

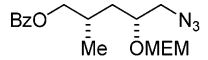


Ethyl 2-((1*S*,6*R*)-4-Methyl-2-oxo-6-(prop-1-en-2-yl)cyclohex-3-enyl)acetate (9). (−)-Isocarvone **8** (4.24 g, 28.2 mmol)

(22) Prepared from the Diels-Alder adduct of **32** through a two-step procedure: TBAF mediated cleavage of the TIPS ether and subsequent bis-*p*-nitrobenzoyl ester formation using *p*-nitrobenzoyl chloride, pyridine, and DMAP provided ketoester **35** in 53% yield from **32** as a white solid. Recrystallization was performed in diethyl ether.

(23) See also the Supporting Information.

(24) Azide **36** was obtained in 9 steps from (*R*)-γ-hydroxymethyl-γ-butyrolactone analogously to previously prepared azide

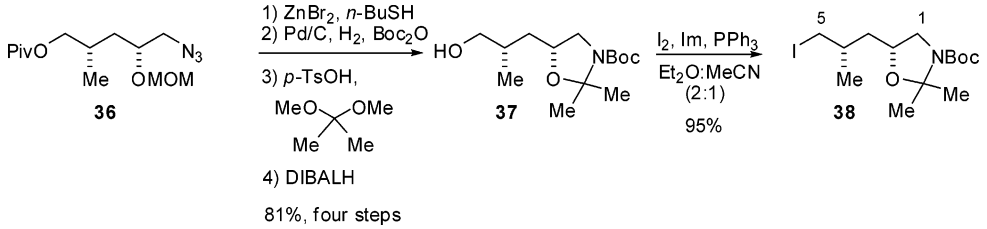


see reference 12b.

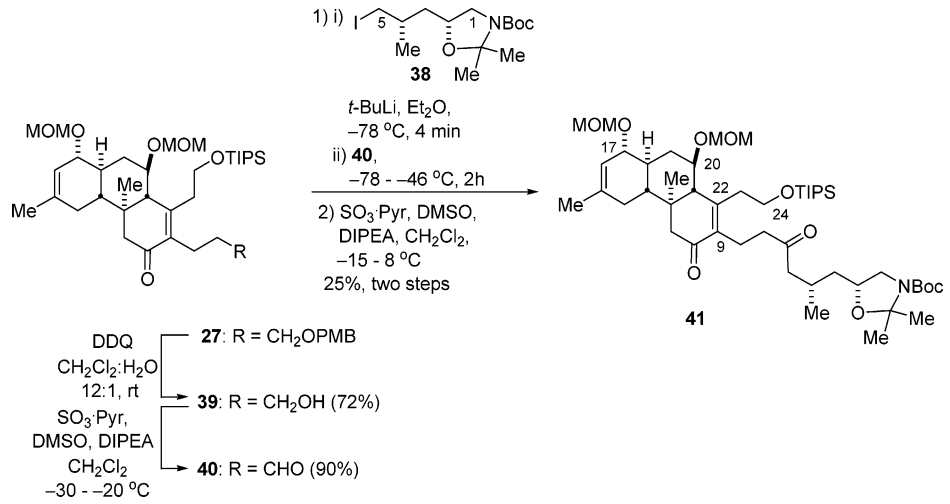
(25) Sohn, J. H.; Waizumi, N.; Zhong, H. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 7290−7291.

(26) See the Supporting Information.

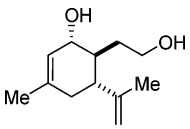
SCHEME 8



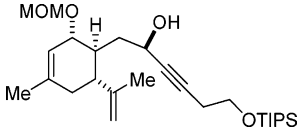
SCHEME 9



was dissolved in anhydrous THF (110 mL) and cooled to −78 °C under argon followed by the addition of LiHMDS (33.9 mL, 33.9 mmol, 1 M in hexanes) to the reaction mixture which was stirred for 1 h. Ethyl bromoacetate (4.95 mL, 42.3 mmol) was added to the reaction mixture and stirred for 4 h then warmed to rt and stirred for 45 min. The reaction mixture was quenched by the addition of sat. aqueous $NaHCO_3$ (100 mL). The aqueous phase was extracted with Et_2O (2 × 100 mL), and the combined organic phases were washed with brine (150 mL), then dried ($MgSO_4$), filtered, and evaporated to dryness in vacuo. The residue was purified using flash column chromatography (20−50:80−50, Et_2O/pentane) providing **9** (5.66 g, 85%) as a colorless oil. **9**: R_f, 0.25 (AcOEt/hexane, 1:4); $[\alpha]^{23}_D$ +12.3 (*c* 1.2, CH_2Cl_2); IR (film) 2977, 1735, 1670, 1439, 1339, 1310, 1215, 1180, 1094, 1032, 902, 867; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (bs, 1H), 4.85 (app. quint, J = 1.6 Hz, 1H), 4.83 (s, 1H), 4.17 (dq, J = 0.9, 7.1 Hz, 2H), 2.79−2.74 (m, 2H), 2.47−2.45 (m, 3H), 2.20 (dd, J = 3.7, 18.0 Hz, 1H), 1.95 (s, 3H), 1.71 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 172.7, 160.7, 144.7, 125.6, 114.4, 60.3, 47.6, 45.3, 36.5, 31.9, 24.1, 18.0, 14.1. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.92; H, 8.53.

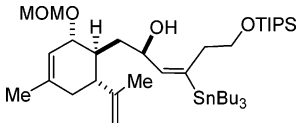


(1*R*,5*R*,6*S*)-6-(2-Hydroxyethyl)-3-methyl-5-(prop-1-en-2-yl)cyclohex-2-enol (10). Ketoester **9** (6.1 g, 25.8 mmol) was dissolved in anhydrous Et_2O (30 mL) and added to a precooled (−78 °C) suspension of $LiAlH_4$ (1.96 g, 51.6 mmol) in Et_2O (90 mL) under argon and stirred for 10 min. The reaction mixture was then warmed to 0 °C and stirred for 1 h followed by removal of the ice bath, and the reaction was then allowed to reach ambient temperature and stirred for 20 min. The reaction was quenched by slow addition of H_2O (2 mL), 15% NaOH(aq) (2 mL), and H_2O (6 mL). The precipitates were filtered off and washed thoroughly with Et_2O (3 × 30 mL) and MeOH (3 × 30 mL). The combined organic phases were evaporated to dryness in vacuo. The residue was purified by flash column chromatography (AcOEt/pentane, 2:3) affording **10** (3.65 g, 72%) as a colorless oil, which crystallized upon standing. **10**: mp 61−62 °C; R_f, 0.20 (AcOEt/pentane, 1:1); $[\alpha]^{23}_D$ +22.2 (*c* 1.5, CH_2Cl_2); IR (film) 3350, 2893, 1644, 1442, 1377, 1162, 1074, 1016, 1006, 894; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (bs, 1H), 4.80−4.76 (m, 2H), 4.02−3.96 (m, 1H), 3.83 (ddd, J = 3.6, 5.7, 10.9 Hz, 1H), 3.82−3.71 (m, 1H), 3.61 (ddd, J = 3.1, 9.3, 11.1 Hz, 1H), 2.23 (ddd, J = 4.9, 11.1, 11.1 Hz, 1H), 2.17−2.04 (m, 1H), 1.88−1.75 (m, 3H), 1.68 (s, 3H), 1.63 (s, 3H), 1.48 (dddd, J = 2.2, 8.7, 8.7, 11.1 Hz, 1H), 1.35 (dddd, J = 3.4, 9.0, 9.0, 14.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 136.1, 124.2, 113.2, 73.5, 62.3, 47.3, 43.4, 35.7, 35.4, 22.9, 17.9; EI-MS [M] 196 m/z. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.22; H, 10.22.

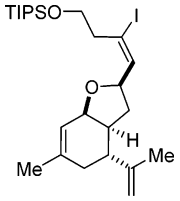


(*R*)-6-(Tri-isopropyl-silyloxy)-1-((1*S*,2*R*,6*R*)-2-(methoxymethoxy)-4-methyl-6-(prop-1-en-2-yl)cyclohex-3-enyl)-hex-3-yne-2-ol (18). A 25 mL round bottomed flask was charged with $Zn(OTf)_2$ (26.4 g, 72.6 mmol), and heated to 120 °C under vacuum for 3 h. After cooling to rt (+)-*N*-methyl-

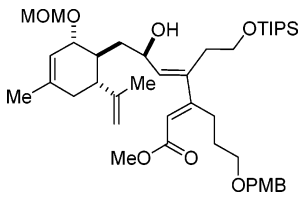
ephedrine (13.2 g, 73.9 mmol) was added under argon, and the flask was purged with argon two times and kept under vacuum for 15 min. Anhydrous toluene (12 mL) followed by triethylamine (10.2 mL) was added and after 2 h (but-3-ynyloxy)-triisopropylsilane (**17**) (15.6 g, 68.9 mmol) was added in one portion. After 1 h aldehyde **16** (5.03 g, 21.1 mmol) was added in one portion at rt and stirred under argon. The reaction mixture was stirred for 15 h upon which the reaction mixture had turned yellowish. The mixture was diluted with AcOEt (100 mL) and washed with sat. aqueous NH_4Cl (2 × 50 mL). The combined aqueous phases were back-extracted with AcOEt (3 × 50 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography (Et_2O/pentane, 1:4−1:2) providing propargylic alcohol **18** (7.6 g, 78%) as a colorless oil and as a single diastereomer. (But-3-ynyloxy)triisopropylsilane **17** (8.0 g, 51%) was recovered. **18**: R_f, 0.21 (Et_2O/pentane, 1:2); $[\alpha]^{23}_D$ +46.1 (*c* 2.0, CH_2Cl_2); IR (film) 3420, 3072, 2985, 2874, 2725, 1711, 1680, 1643, 1463, 1382, 1333, 1215, 1093, 1041, 892, 812, 737, 681; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 (bs, 1H), 4.84−4.79 (m, 3H), 4.70 (d, J = 7.0 Hz, 1H), 4.47−4.41 (m, 1H), 4.00−3.94 (m, 1H), 3.76 (t, J = 7.4 Hz, 2H), 3.43 (s, 3H), 3.38 (bs, 1H), 2.44 (ddd, J = 1.9, 7.6, 7.6, 2H), 2.28 (ddd, J = 5.1, 11.2, 11.2 Hz, 1H), 2.17−2.05 (m, 1H), 1.95 (ddd, J = 1.9, 5.3, 13.6 Hz, 1H), 1.84 (dd, J = 5.1, 17.6 Hz, 1H), 1.76−1.59 (m, 8H), 1.05 (s, 18H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 136.8, 121.7, 113.7, 95.7, 82.9, 81.3, 80.9, 62.2, 62.1, 56.2, 47.4, 40.6, 39.0, 35.9, 23.2, 23.0, 18.2, 17.9, 11.9. Anal. Calcd for $C_{27}H_{48}O_4Si$: C, 69.78; H, 10.41. Found: C, 69.57; H, 10.63.



(2*R*,3*E*)-4-(Tributylstannyl)-6-(tri-isopropyl-silyloxy)-1-((1*S*,2*R*,6*R*)-2-(methoxymethoxy)-4-methyl-6-(prop-1-en-2-yl-)cyclohex-3-enyl)hex-3-en-2-ol (19). To propargylic alcohol **18** (7.7 g, 16.7 mmol) and dichlorobis(tris(*o*-toloyl)phosphine)-palladium(II) (132 mg, 0.01 mmol) in THF (17 mL) at 0 °C was added dropwise tributyltin hydride (8 mL, 29.7 mmol) over a period of 0.45 h followed by removal of the ice bath allowing the reaction mixture to reach rt. The reaction mixture was purified directly by flash column chromatography (Et_2O/pentane, 1:9−1:2) affording **19** (11.96 g, 95%) as a colorless oil. **19**: R_f 0.56 (Et_2O/pentane, 1:2); $[\alpha]^{23}_D$ +31.1 (*c* 2.0, $CDCl_3$); IR (film) 3456, 2924, 1645, 1464, 1377, 1292, 1248, 1214, 1150, 1096, 1036, 919, 883, 782, 687; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (d, J = 7.7 Hz, 1H), 5.47 (s, 1H), 4.85 (s, 1H), 4.84 (d, J = 7.0 Hz, 1H), 4.80 (s, 1H), 4.71 (d, J = 7.0 Hz, 1H), 4.57 (bs, 1H), 3.94 (d, J = 7.8 Hz, 1H), 3.69−3.53 (m, 2H), 3.45 (s, 3H), 3.42 (d, J = 2.3 Hz, 1H), 2.70 (ddd, J = 7.9, 7.9, 12.6 Hz, 1H), 2.42 (ddd, J = 5.0, 8.4, 13.5 Hz, 1H), 2.26 (ddd, J = 4.9, 10.9, 10.9 Hz, 1H), 2.18−2.05 (m, 1H), 1.85 (dd, J = 4.6, 17.2 Hz, 1H), 1.71 (m, 10H), 1.64−1.40 (m, 8H), 1.30 (sextet, J = 7.2 Hz, 6H), 1.07 (s, 18H), 1.05 (s, 3H), 0.88 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 140.9, 136.7, 121.8, 113.5, 95.6, 80.9, 67.0, 63.2, 56.1, 47.7, 39.8, 39.1, 37.3, 35.8, 29.1, 27.4, 23.0, 18.5, 18.0, 13.7, 11.9, 9.6. Anal. calcd for $C_{39}H_{76}O_4SiSn$: C, 61.98; H, 10.14. Found: C, 62.05; H, 10.11.

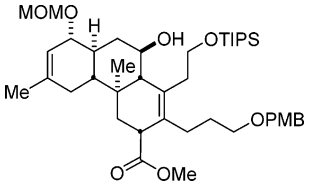


((3*E*)-4-((2*R*,3a*S*,4*R*,7a*S*)-2,3,3a,4,5,7a-Hexahydro-6-methyl-4-(prop-1-en-2-yl)benzofuran-2-yl)-3-iodobut-3-enyloxy)-triisopropylsilane (21). A solution of the β-stannylated allylic alcohol **19** (664 mg, 0.88 mmol) in CH_2Cl_2 (30 mL) was cooled to −78 °C and a solution of iodine (178 mg, 0.97 mmol, CH_2Cl_2 (20 mL)) was added at once, stirred under argon for 15 min, and then poured into a sat. aqueous sodium thiosulfate solution (10 mL). The aqueous phase was back-extracted with CH_2Cl_2 (10 mL), and the combined organic phases were evaporated to dryness and subjected to flash column chromatography on demetalated silica gel (Et_2O/pentane, 1:5) affording **21** (350 mg, 75%, contaminated with $ISnBu_3$) and iodide **20** (67 mg, 13%) both as colorless oils. **21**: R_f, 0.82 (Et_2O/pentane, 1:2); $[\alpha]^{23}_D$ +14.1 (*c* 1.5, $CHCl_3$); IR (film) 2956, 1642, 1457, 1378, 1248, 1105, 883, 743, 682; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (d, J = 8.0 Hz, 1H), 5.61 (bs, 1H), 4.82 (m, 1H), 4.76 (s, 1H), 4.55 (ddd, J = 7.8, 7.8, 8.0 Hz, 1H), 4.06 (bs, 1H), 3.79 (app. t, J = 7.0 Hz, 2H), 2.82 (ddd, J = 7.0, 7.0, 14.1 Hz, 1H), 2.61 (dddd, J = 0.9, 7.0, 7.0, 14.1 Hz, 1H) 2.26−2.16 (m, 1H), 2.12−2.07 (m, 2H), 1.96−1.91 (m, 2H), 1.75 (s, 3H), 1.67 (s, 3H), 1.67−1.59 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 144.1, 140.5, 118.7, 112.4, 102.1, 76.1, 75.4, 62.2, 45.1, 42.9, 39.1, 36.6, 35.8, 29.1, 26.6, 23.6, 19.4, 18.0, 16.4, 13.6, 11.9; HRMS (ESI) calcd for [M + H^+], 531.215; found, 531.2153.

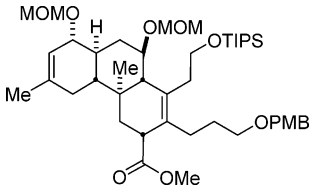


(6*R*,2*E*,4*E*)-Methyl 3-(3-(4-Methoxybenzyloxy)propyl)-6-hydroxy-4-(2-(tri-isopropyl-silyloxy)-ethyl)-7-((1*S*,2*R*,6*R*)-2-(methoxymethoxy)-4-methyl-6-(prop-1-en-2-yl)cyclohex-3-enyl)hepta-2,4-dienoate (24). A solution of the β-stannylated allylic alcohol **19** (1.97 g 2.6 mmol) in Et_2O (160 mL) was cooled to 0 °C, and a solution of iodine (1.0 g, 4.0 mmol, in 55 mL of Et_2O) was added at once and stirred under argon for 15 min. The reaction mixture was quenched by the addition of sat. sodium thiosulfate solution (100 mL), the aqueous phase was back-extracted with Et_2O (50 mL), and the combined organic phases were evaporated to dryness and purified by flash column chromatography on silica gel (Et_2O/pentane, 2:3) to give iodide **20**, which was used immediately for the next reaction. A 50 mL Schlenk tube was charged with tetrakis(triphenylphosphine)palladium(0) (300 mg, 0.26 mmol) and copper(I)chloride (257 mg, 2.6 mmol), and the mixture was degassed under high vacuum with an argon purge. Iodide **20** and stannane **23** (2.88 g, 5.2 mmol) were dissolved in THF/NMP (1:1, 24 mL) degassed by bubbling argon through the solution for 5 min and then added to the Schlenk flask containing the salts, which was precooled to −78 °C. The mixture was subjected to high vacuum for 1 min and the flask was back-filled with argon. The reaction

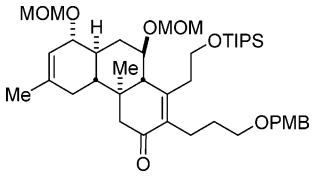
mixture was stirred at rt for 2 h, and then more tetrakis-(triphenylphosphine)palladium(0) (70 mg, 0.061 mmol, dissolved in 0.5 mL THF) was added. The mixture was stirred for 1 h, then more tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.026 mmol) was added as a solid, and the mixture was stirred for an additional 1 h. More tetrakis(triphenylphosphine)-palladium(0) (30 mg, 0.026 mmol) and CuCl (25 mg, 0.25 mmol) was added, and the reaction mixture was stirred for an additional 1.5 h, then the reaction mixture was diluted with diethyl ether (150 mL) and washed with H_2O (2 × 100 mL). The aqueous layer was further extracted with diethyl ether (2 × 150 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (Et_2O/pentane (1:2−2:1) and AcOEt/CH_2Cl_2, (1:9−3:7)) affording coupling product **24** (1.56 g, 82%, two steps) as a colorless oil. **24**: R_f, 0.22 (AcOEt/CH_2Cl_2, 1:9); $[\alpha]^{23}_D$ +33.7 (*c* 4.0, CH_2Cl_2); IR (film) 3441, 2942, 1717, 1616, 1516, 1456, 1378, 1247, 1167, 1097, 887, 820, 681; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.85 (s, 1H), 5.78 (d, J = 8.1 Hz, 1H), 5.47 (bs, 1H), 4.86−4.79 (m, 3H), 4.70 (d, J = 7.0 Hz, 1H), 4.53−4.45 (m, 1H), 4.42 (s, 2H), 3.93 (d, J = 8.5 Hz, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 3.67−3.53 (m, 3H), 3.47 (t, J = 6.5 Hz, 2H), 3.43 (s, 1H), 2.97−2.74 (m, 2H), 2.62 (ddd, J = 7.6, 7.6, 14.4 Hz, 1H), 2.47 (ddd, J = 5.4, 7.1, 14.0 Hz, 1H), 2.26 (ddd, J = 4.9, 10.9, 10.9 Hz, 1H), 2.18−2.05 (m, 1H), 1.86 (dd, J = 4.9, 17.2 Hz, 1H) 1.77−1.62 (m, 12H), 1.52 (ddd, J = 6.4, 9.8, 15.9 Hz, 1H), 1.08 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 161.4, 159.0, 146.6, 138.1, 137.0, 136.8, 130.7, 129.2, 121.7, 115.7, 113.7, 112.8, 95.6, 80.7, 72.4, 69.9, 67.8, 62.1, 56.2, 55.2, 51.0, 47.7, 39.6, 39.1, 35.8, 30.8, 29.3, 25.7, 23.0, 18.6, 18.0, 11.9; HRMS calcd for [M + Na], 751.4581; found, 751.4582. Anal. Calcd for $C_{42}H_{68}O_8Si$: C, 69.19; H, 9.40. Found: C, 69.37; H, 9.39.



(3*R*,4a*S*,4b*R*,8*R*,8a*S*,10*R*,10a*S*)-Methyl 2-(3-(4-Methoxybenzyloxy)propyl)-3,4,4a,4b,5,8,8a,9,10,10a-decahydro-10-hydroxy-1-(2-(tri-isopropyl-silyloxy)-ethyl)-8-(methoxymethoxy)-4a,6-dimethylphenanthrene-3-carboxylate (25). A solution of IMDA precursor **24** (245 mg, 0.336 mmol) in toluene (20 mL) was degassed by bubbling argon through the solution for 2 min then heated to 205 °C for 28 h in a sealed Carius tube. The reaction mixture was evaporated to dryness and purified using silica gel column chromatography (AcOEt/CH_2Cl_2, 1:7−1:4) providing IMDA adduct **25** (209 mg, 85%) as a colorless oil. **25:** R_f, 0.41 (Et_2O/pentane, 3:2); $[\alpha]^{23}_D$ −24.7 (*c* 3.5, CH_2Cl_2); IR (film) 3426, 2945, 1734, 1613, 1513, 1465, 1363, 1302, 1248, 1151, 1094, 1040, 918, 883, 821, 735, 686; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 8.0 Hz, 2H), 5.42 (bs, 1H), 4.77 (d, J = 6.9 Hz, 1H), 4.69 (d, J = 6.9 Hz, 1H), 4.40 (bs, 3H), 3.94−3.83 (m, 3H), 3.80 (s, 3H), 3.76 (d, J = 8.0 Hz, 1H), 3.66 (s, 3H), 3.42 (s, 3H), 3.39 (t, J = 6.1 Hz, 2H), 3.12 (app. t, J = 6.8 Hz, 1H), 2.81−2.75 (m, 1H), 2.70−2.63 (m, 1H), 2.55 (app. dt, J = 3.9, 3.9, 13.1 Hz, 1H) 2.30−2.15 (m, 2H), 1.90−1.77 (m, 4H), 1.67 (s, 3H), 1.66−1.56 (m, 3H), 1.30−1.23 (m, 1H), 1.14−1.08 (m, 2H), 1.05−1.02 (m, 21H), 0.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 159.0, 136.3, 134.7, 131.7, 130.6, 129.1, 122.1, 113.6, 96.6, 81.5, 72.4, 69.7, 66.7, 65.0, 55.6, 55.4, 55.2, 51.7, 46.0, 43.0, 41.0, 38.5, 37.9, 31.3, 30.2, 28.5, 27.6, 23.5, 17.91, 17.86, 16.4, 11.8. HRMS (ESI) calcd for $C_{42}H_{68}O_8SiNa$ [M + Na], 751.4576; found, 751.4581.

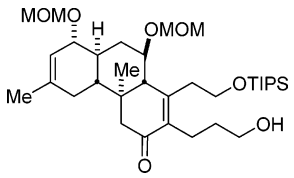


(3*R*,4a*S*,4b*R*,8*R*,8a*S*,10*R*,10a*S*)-Methyl 2-(3-(4-Methoxybenzyloxy)propyl)-3,4,4a,4b,5,8,8a,9,10,10a-decahydro-1-(2-(tri-isopropyl-silyloxy)-ethyl)-8,10-bis(methoxymethoxy)-4a,6-dimethylphenanthrene-3-carboxylate (26). To a solution of **25** (350 mg, 0.48 mmol) in CH_2Cl_2 (3.5 mL) under argon was added *N*,*N*-diisopropylethylamine (2 mL, 11.5 mmol) and methoxymethyl chloride (0.73 mL, 9.6 mmol), and the reaction mixture was stirred for 2 h resulting in a slightly yellow coloration. The reaction mixture was purified directly by flash column chromatography on silica gel (Et_2O/pentane, 2:3) providing the title compound **26** (341 mg, 92%) as a colorless oil. **26:** R_f, 0.76 (Et_2O/pentane, 3:2); $[\alpha]^{23}_D$ −3.2 (*c* 5.2, CH_2Cl_2); IR (film) 2942, 1739, 1613, 1513, 1465, 1378, 1363, 1302, 1248, 1151, 1101, 1041, 922, 883, 819, 681; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.41 (bs, 1H), 4.82−4.78 (m, 3H), 4.65 (d, J = 7.0 Hz, 1H), 4.40 (s, 2H), 3.82−3.72 (m, 6H), 3.68−3.63 (m, 4H), 3.44 (s, 3H), 3.39−3.32 (m, 4H), 3.12 (app. t, J = 8.1 Hz, 1H), 2.90 (ddd, J = 4.3, 4.3, 12.8 Hz, 1H), 2.70−2.63 (m, 1H), 2.32−2.16 (m, 3H), 1.90−1.82 (m, 3H), 1.78 (dd, J = 7.4, 13.5 Hz, 1H), 1.68 (s, 3H), 1.65−1.52 (m, 4H), 1.31 (ddd, J = 6.1, 10.2, 12.0 Hz, 1H), 1.14−1.02 (m, 23H), 0.70 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 175.0, 159.6, 135.7, 133.7, 133.6, 131.3, 129.4, 122.6, 114.0, 97.3, 95.7, 80.6, 76.6, 72.8, 70.2, 63.7, 59.8, 55.7, 55.4, 54.7, 52.8, 51.3, 44.9, 44.2, 40.2, 39.0, 37.9, 34.0, 30.7, 30.3, 27.9, 23.5, 18.40, 18.38, 12.4; HRMS (ESI) calcd for $C_{44}H_{72}O_9SiNa$ [M + Na], 795.4843; found, 795.4825.

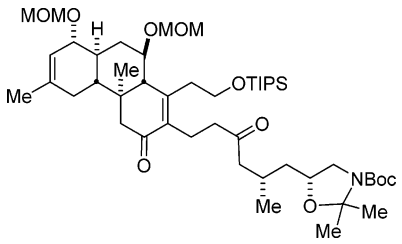


(4a*S*,4b*R*,8*R*,8a*S*,10*R*,10a*S*)-2-(3-(4-Methoxybenzyloxy)-propyl)-4,4a,4b,5,8a,9,10,10a-octahydro-1-(2-(tri-isopropyl-silyloxy)-ethyl)-8,10-bis(methoxymethoxy)-4a,6-dimethyl-phenanthren-3(8*H*)-one (27). To a yellow solution of KHMDS (1.7 mmol, in 3.4 mL toluene, 0.5 M) at −78 °C under argon was added ester **26** (658 mg, 0.85 mmol) in toluene (2 mL + 1.4 mL rinse). The reaction mixture was stirred for 2 min and then triethylphosphite (0.3 mL, 1.7 mmol) was added. The mixture was stirred for 2 min, and then the argon was exchanged for an O_2 atmosphere. The reaction mixture was stirred at −78 °C for 1.25 h, then quenched by the addition of sat. aqueous $NaHCO_3$ (10 mL). The mixture was transferred to a separation funnel containing Et_2O (50 mL) and H_2O (30 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), and the combined

organic phases were washed with sat. aqueous NH_4Cl (20 mL) and brine (20 mL), then dried ($MgSO_4$), filtered, and evaporated in vacuo. A small portion of α-hydroxy ester **27a** was subjected to silica gel column chromatography (pentane/Et_2O; 3:2−2:3), and the major diastereomer was eluted free of its epimer and characterized, but in practice the crude mixture was taken to the next step. **27a**: R_f, 0.34 (Et_2O/pentane, 3:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.41 (bs, 1H), 4.84−4.77 (m, 5H), 4.64 (d, J = 7.0 Hz, 1H), 4.39 (s, 2H), 3.88−3.82 (m, 2H), 3.80 (s, 3H), 3.73 (s, 3H), 3.71−3.65 (m, 2H), 3.44 (s, 3H), 3.42−3.36 (m, 7H), 2.91 (ddd, J = 4.0, 4.0, 8.1 Hz, 1H), 2.78−2.67 (m, 1H), 2.52 (d, J = 11.0 Hz, 1H), 2.41−2.26 (m, 2H), 2.06 (d, J = 14.4 Hz, 1H), 2.03−1.93 (m, 1H), 1.83−1.74 (m, 3H), 1.66 (s, 3H), 1.59 (s, 3H),1.54−1.45 (m, 1H), 1.14 (app. q, J = 11.8 Hz, 1H), 1.08−0.98 (m, 23H), 0.79 (s, 3H); ^{13}C NMR (50 MHz, C_6D_6) δ 177.3, 159.2, 138.2, 136.2, 134.0, 132.8, 129.3, 129.2, 126.4, 121.5, 113.7, 96.9, 95.7, 80.3, 75.5, 72.5, 70. 2, 62.7, 55.9, 55.6, 55.2, 52.7, 50.1, 47.1, 40.5, 38.7, 36.8, 33.6, 29.8, 29.7, 26.9, 23.4, 18.1, 16.1, 12.0; HRMS (ESI) calcd for $C_{44}H_{72}O_{10}SiNa$ [M + Na], 811.4787; found, 811.4777. The α-hydroxy ester **27a** (crude product) was dissolved in THF (3.4 mL) and cooled to −78 °C followed by dropwise addition of lithium aluminum hydride (3.4 mL, 3.4 mmol, 1 M in THF) and stirred for 2 min, then warmed to rt and stirred for 1.25 h. The reaction was cooled to 0 °C and phosphate buffer (pH = 7.000 ± 0.010, Radiometer analytical, Na_2HPO_4 27.5 mmol/L and KH_2PO_4 20.0 mmol/L, Germicides, 4 mL) was added dropwise (violent gas evolution), and the mixture was stirred for 2 min. Then THF (2 mL) and $NaIO_4$ (960 mg, 4.5 mmol) were added, and the reaction was stirred for 1.75 h. Then more $NaIO_4$ (330 mg, 1.5 mmol) was added, and the reaction was stirred for 0.5 h.The temperature was then raised to 28 °C, and the mixture was stirred for 0.5 h. More $NaIO_4$ (170 mg, 0.80 mmol) was then added. The reaction mixture was stirred for 55 min then more $NaIO_4$ (170 mg, 0.80 mmol) was added and stirred for 50 min after which full conversion based on TLC analysis was achieved. The reaction mixture was partitioned between Et_2O (50 mL) and H_2O (50 mL). The aqueous phase was extracted with Et_2O (4 × 20 mL), then brine was added to the aqueous phase and further extracted with AcOEt (2 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to dryness in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane, 1:2) providing enone **27** (489 mg, 79% from **26**) as a colorless oil. **27**: R_f, 0.43 (Et_2O/pentane, 3:2); $[\alpha]^{23}_D$ −18.7 (*c* 1.7, CH_2Cl_2); IR (film) 2942, 1662, 1616, 1516, 1464, 1380, 1248, 1096, 922, 884, 821, 737, 685; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.43 (bs, 1H), 4.84−4.75 (m, 3H), 4.64 (d, J = 7.1 Hz, 1H), 4.41 (s, 2H), 3.91 (ddd, J = 4.7, 9.2, 9.2 Hz, 1H), 3.79 (s, 3H), 3.78−3.75 (m, 1H), 3.72−3.63 (m, 2H), 3.45−3.37 (m, 8H), 2.97 (ddd, J = 4.0, 4.0, 13.0 Hz, 1H), 2.92−2.82 (m, 1H), 2.56−2.45 (m, 3H), 2.42 (d, J = 10.6 Hz, 1H), 2.33 (ddd, J = 6.5, 9.4, 13.4 Hz, 1H), 2.07 (d, J = 17.1 Hz, 1H), 1.83−1.74 (m, 2H), 1.67 (s, 3H), 1.66−1.38 (m, 3H), 1.19 (app. q, J = 12.0, 1H), 1.10−0.99 (m, 22H), 0.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2, 159.0, 155.8, 138.1, 135.8, 130.6, 129.3, 121.5, 113.6, 96.9, 95.6, 80.6, 79.8, 76.1, 72.3, 69.8, 62.2, 56.1, 55.6, 55.2, 52.5, 51.6, 45.8, 41.0, 36.0, 35.6, 29.3, 29.0, 23.4, 22.2, 18.0, 13.8, 11.8; HRMS (ESI) calcd for $C_{42}H_{68}O_8SiNa$ [M + Na], 751.4601; found, 751.4581.



(4a*S*,4b*R*,8*R*,8a*S*,10*R*,10a*S*)-4,4a,4b,5,8a,9,10,10a-Octahydro-1-(2-(tri-isopropyl-silyloxy)-ethyl)-2-(3-hydroxypropyl)-8,10-bis(methoxymethoxy)-4a,6-dimethylphenanthren-3(8*H*)-one (39). Enone **27** (29.6 mg, 0.041 mmol) was dissolved in a mixture of CH_2Cl_2 (1 mL) and H_2O (0.08 mL). DDQ (14.0 mg, 0.062 mmol) was added to the reaction mixture in one portion and stirred vigorously for 30 min. Aqueous sat. $NaHCO_3$ (10 mL) was added, and the reaction mixture was stirred for 5 min. The mixture was partitioned between Et_2O (30 mL) and H_2O (20 mL). The organic phase was washed with H_2O (20 mL), and the combined aqueous phases were back-extracted with Et_2O (2 × 10 mL). The combined organic phases were washed with brine (20 mL) and dried (Na_2SO_4), filtered, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography (Et_2O/pentane, 1:1−0-1) affording **39** (17.9 mg, 72%) as a colorless oil. **39**: mp 82−83 °C; R_f, 0.38 (AcOEt/heptane, 3:2); $[\alpha]^{23}_D$ −21.6 (*c* 7.0, CH_2Cl_2); IR (film) 3459, 2941, 1653, 1595, 1559, 1465, 1379, 1211, 1150, 1101, 1041, 923, 883, 786, 728, 681, 658; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51 (bs, 1H), 4.81 (d, J = 7.0 Hz, 1H), 4.75 (d, J = 7.0 Hz, 1H), 4.64 (d, J = 7.0 Hz, 1H), 4.59 (d, J = 7.0 Hz, 1H), 4.06 (ddd, J = 4.7, 9.2, 9.2 Hz, 1H), 3.83−3.72 (m, 2H), 3.68−3.50 (m, 2H), 3.42 (ddd, J = 5.1, 10.6, 10.6 Hz, 1H), 3.34 (s, 3H), 3.28 (s, 3H), 3.05 (ddd, J = 4.6, 4.6, 13.1 Hz, 1H), 2.97−2.83 (m, 2H), 2.78 (app. t, J = 5.6 Hz, 1H), 2.60−2.44 (m, 2H), 2.39 (d, J = 16.9 Hz, 1H), 2.20 (d, J = 10.5 Hz, 1H), 1.77 (d, J = 16.9 Hz, 1H), 1.76−1.61 (m, 2H), 1.57−1.47 (m, 4H), 1.41 (d, J = 7.8 Hz, 2H), 1.15−0.97 (m, 23H), 0.53 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 197.5, 156.2, 138.3, 135.0, 122.6, 97.2, 95.7, 80.1, 76.5, 62.8, 61.6, 55.9, 55.4, 52.8, 51.6, 45.7, 41.0, 39.2, 36.2, 33.0, 29.2, 23.5, 21.6, 18.3, 13.8, 12.3; HRMS (ESI) calcd for $C_{34}H_{60}O_7SiNa$ [M + Na^+], 631.4001; found, 631.4005.



(4a*S*,4b*R*,8*R*,8a*S*,10*R*,10a*S*)-4,4a,4b,5,8a,9,10,10a-Octahydro-1-(2-(tri-isopropyl-silyloxy)-8,10-bis(methoxymethoxy)-4a,6-dimethyl-2-((*S*)-5-methyl-6-((*R*)-2,2-dimethyloxazolidin-5-yl)-3-oxohexyl)phenanthren-3(8H)-one (41). Alcohol **39** (48.7 mg, 0.080 mmol) was dissolved in CH_2Cl_2 (0.5 mL), and the reaction was cooled to −30 °C and DIPEA (54 μL, 0.32 mmol) and DMSO (60 μL) were added. Sulfurtrioxide pyridine complex (SO_3·pyr) (38 mg, 0.24 mmol) was dissolved in DMSO (150 μL) and added dropwise to the reaction mixture and stirred for 20 min while warming to −20 °C. The reaction was purified directly by flash column chromatography (AcOEt/pentane, 1:4) providing **40** (43.9 mg, 90%) as a colorless oil. **40:** R_f, 0.59 (AcOEt/heptane, 3:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (s, 1H), 5.53 (bs, 1H), 4.80−4.76 (m, 2H), 4.61 (d, J = 7.0 Hz,

1H), 4.60 (d, $J = 7.0$ Hz, 1H), 4.04 (ddd, $J = 4.7, 9.1, 9.1$ Hz, 1H), 3.82−3.73 (m, 2H), 3.42 (ddd, $J = 4.9, 11.4, 11.4$ Hz, 1H), 3.35 (s, 3H), 3.28 (s, 3H), 3.07 (ddd, $J = 5.1, 5.1, 13.3$ Hz, 1H), 3.00−2.71 (m, 3H), 2.50−2.43 (m, 1H), 2.39 (d, $J = 16.9$ Hz, 1H), 2.30−2.23 (m, 2H), 2.18 (d, $J = 10.7$ Hz, 1H), 1.75 (d, $J = 16.9$ Hz, 1H), 1.58−1.47 (m, 4H), 1.42−1.36 (m, 2H), 1.15−0.91 (m, 23H), 0.53 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 200.1, 196.0, 155.7, 137.2, 135.0, 122.6, 97.1, 95.7, 80,1, 76.3, 62.8, 55.9, 55.4, 52.8, 51.6, 45.7, 43.6, 41.0, 39.2, 36.2, 36.1, 29.1, 23.4, 19.3, 18.3, 13.7, 12.3. Iodide **38** (43.3 mg, 0.11 mmol) was dissolved in Et_2O (0.2 mL) and cooled to −78 °C, then *t*-BuLi (146 μL, 0.25 mmol) was added, and the resulting mixture was stirred for 4 min at −78 °C under an argon atmosphere. Then aldehyde **40** (43.9 mg, 0.072 mmol) was dissolved in Et_2O (0.2 mL) and added to lithiated **38** and stirred for 2 h from −78 to −46 °C. The reaction mixture was quenched by the addition of sat. aqueous NH_4Cl (0.1 mL) and warmed to rt. The mixture was purified directly by flash column chromatography (AcOEt/hexane, 1:2) providing a diastereomeric and rotameric mixture of alcohols (32.3 mg, 52%). The diastereomeric mixture of alcohols (32.3 mg, 0.037 mmol) was dissolved in CH_2Cl_2 (0.25 mL), the solution was cooled to −15 °C, and *N*,*N*-diisopropylethylamine (27 μL, 0.16 mmol) and DMSO (30 μL) was added. SO_3·pyr (19 mg, 0.12 mmol) was dissolved in DMSO (75 μL) and added dropwise to the reaction mixture, and the mixture was stirred for 1 h while the temperature reached 8 °C. The reaction was purified directly by flash column chromatography (AcOEt/pentane, 1:4) affording diketone **41** (15.4 mg, 25% from **40**) as a colorless oil. **41**: R_f, 0.51 (AcOEt/heptane, 1:1); $[\alpha]^{23}_D$ 1.8 (*c* 0.4, CH_2Cl_2); IR (film) 2939, 1700, 1653, 1465, 1395, 1151, 1101, 1042, 922, 882; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44 (bs, 1H), 5.82 (d, $J = 7.0$ Hz, 1H) 4.81 (d, $J = 7.1$ Hz, 1H), 4.76 (d, $J = 7.0$ Hz, 1H), 4.65 (d, $J = 7.1$ Hz, 1H), 4.10−3.87 (m, 2H), 3.78 (d, $J = 9.0$ Hz, 1H), 3.75−3.60 (m, 3H), 3.44 (s, 3H), 3.38 (s, 3H), 3.03−2.95 (m, 2H), 2.89−2.79 (m, 1H), 2.75−2.53 (m, 3H), 2.50−2.38 (m, 4H), 2.09 (dd, $J = 2.5, 17.0$ Hz, 1H), 1.83−1.75 (m, 1H), 1.68 (m, 5H), 1.56−1.44 (m, 16H), 1.19 (app. q, $J = 12.0$ Hz, 1H), 1.07−1.01 (m, 27H), 0.94 (d, $J = 6.5$ Hz, 3H), 0.83 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 201.7, 197.2, 157.4, 156.9, 137.0, 136.6, 135.7, 121.6, 96.8, 95.7, 79.9, 75.9, 62.2, 56.1, 55.7, 52.7, 51.7, 51.2, 45.8, 43.3, 41.2, 41.1, 39.8, 38.8, 38.7, 36.1, 35.8, 29.0, 28.4, 27.3, 26.4, 25.2, 24.3, 23.4, 20.4, 20.0, 18.8, 18.0, 13.9, 11.9; HRMS (ESI) calcd for $C_{49}H_{84}NO_{12}Si$ [M + HCOO-], 906.5768; found, 906.5750.

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Supporting Information Available: Experimental details for the synthesis of **11**, **14**−**16**, **22**, **23**, **29**−**32**, **33a**, **33**, **37**, and **38**; copies of ^{1}H NMR and/or ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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