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A General Route toward the Synthesis of the Cladiellin Skeleton Utilizing a SmI_2-Mediated Cyclization

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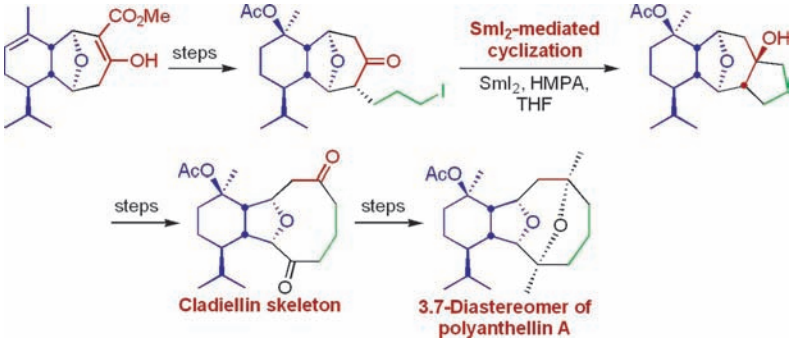

An efficient synthesis of the cladiellin skeleton is reported utilizing methods that were previously developed in this laboratory. The approach is based on a SmI_2-mediated cyclization reaction for the construction of the oxacyclononane unit. A [4 + 3] annulation strategy was used to create the octahydroisobenzofuran moiety. This route provides the cladiellin skeleton in only 14 steps without the use of protecting groups. The present approach also enabled the synthesis of the 3,7-diastereomer of the natural product polyanthellin A.

Introduction

Cladiellin diterpenes belong to a family of marine metabolites isolated from gorgonians and soft corals.[1] The first member of this family, eunicellin, was isolated by Djerassi and co-workers in 1968, and since then more than 60 cladiellin natural products have been reported.[1,2] Cladiellins possess unique structural features: a rare oxabicyclic ring system that is composed of an octahydroisobenzofuran moiety and an oxacyclononane unit (Figure 1).[1] Furthermore, these molecules contain at least six stereogenic centers. In addition to their intriguing structure, several members of this family exhibit interesting biological activity such as cytotoxic activity, antiinflammatory effects, and antimalarial properties.[1] The challenging structure of these compounds, coupled with their diverse biological properties, has made them attractive synthetic targets for several research groups.[3−13]

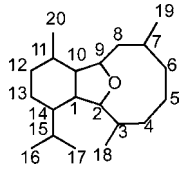

FIGURE 1. Cladiellin skeleton.

Construction of medium-sized ring compounds is often problematic, and there are only a limited number of methods

(1) Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531−556.
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(3) Bernardelli, P.; Moradei, O. M.; Friedrich, D.; Yang, J.; Gallou, F.; Dyck, B. P.; Doskotch, R. W.; Lange, T.; Paquette, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 9021−9032.
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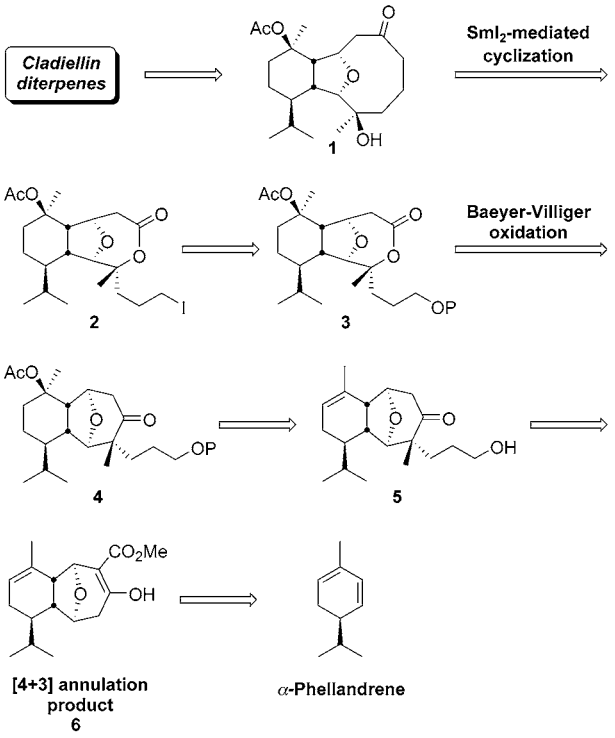
SCHEME 1. First Synthetic Approach to the Cladiellin Skeleton



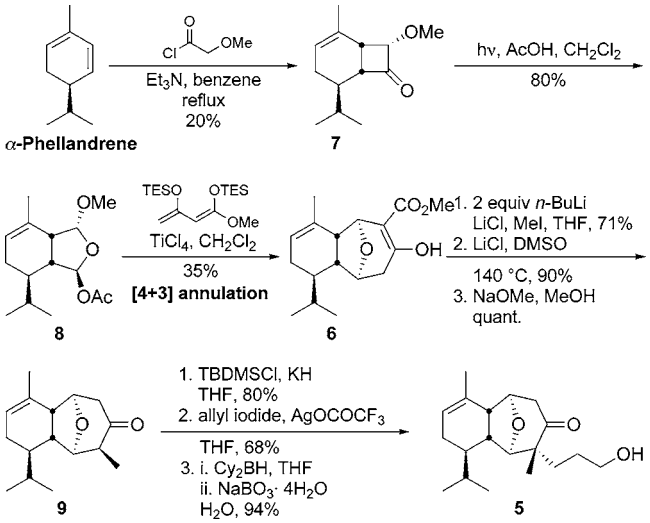
available for creating these systems. It was demonstrated previously that medium-sized rings can be efficiently synthesized by SmI_2-mediated cyclization.[14−16] The focus of the present research was to devise a concise route toward the synthesis of the cladiellin skeleton wherein a SmI_2-mediated cyclization was utilized to create the oxacyclononane subunit. For constructing the octahydroisobenzofuran moiety, a [4 + 3] annulation reaction was employed.[13,17]

Results and Discussion

The initial synthetic approach is depicted in Scheme 1. The strategy was based on a SmI_2-mediated acyl substitution reaction, a method that was developed and widely studied in this group, to create the oxacyclononane subunit of the skeleton.[16] The SmI_2-mediated cyclization precursor **2** was envisioned to derive from hydroxy lactone **3** that in turn could be derived from tricyclic ketone **4** via a Baeyer−Villiger oxidation. The tertiary acetoxy functionality at the C-11 position is prevalent in several cladiellin diterpene natural products, and this functional group was to be introduced at this stage of the synthesis. Compound **5** could be obtained from [4 + 3] annulation product **6**.

The initial steps of the sequence are depicted in Scheme 2. The [4 + 3] annulation product **6** was synthesized following a

SCHEME 2. Initial Steps of the Synthesis



previously developed procedure.[13] According to this route, compound **6** could be obtained in only three steps from commercially available (*R*)-(−)-α-phellandrene. First, (*R*)-(−)-α-phellandrene was reacted in a [2 + 2] ketene olefin cycloaddition.[18] This reaction was followed by a photorearrangement to provide bis-acetal **8**.[19−21] Tricycle **6** could be formed by a $TiCl_4$-mediated [4 + 3] annulation reaction between bis-acetal **8** and 1-methoxy-1,3-bis(triethylsilanyloxy)-1,3-butadiene.[17] Subsequent methylation of the dianion derived from the [4 + 3] annulation product **6**, Krapcho decarboxylation, and epimerization led to the desired methyl ketone **9**.[13,22] The next task was to create the quaternary carbon stereocenter *alpha* to the carbonyl. Direct allylation of the anion derived from methyl ketone **9** proved to be problematic due to decomposition of the substrate under various conditions. Eventually, this transformation could be realized in a two-step sequence. Treatment of α-methyl ketone **9** with potassium hydride and *tert*-butyldimethylsilyl chloride provided the thermodynamic silyl enol ether with high regioselectivity. Introduction of the allyl group was achieved via a silver trifluoroacetate-mediated allylation using allyl iodide.[23] Subsequently, the primary hydroxyl functionality was formed through a chemoselective hydroboration of the terminal alkene with dicyclohexylborane in the presence of the trisubstituted double bond and the ketone providing compound **5**.[24,25]

Previous studies had indicated that some compounds containing the 8-oxabicylo[3.2.1]octa-3-one subunit, as in structure **5**, do not undergo Baeyer−Villiger oxidation readily.[26] However, the viability of this transformation was tested again using

(12) Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, *126*, 10264−10266.
(13) Molander, G. A.; St. Jean, D. J., Jr.; Haas, J. *J. Am. Chem. Soc.* **2004**, *126*, 1642−1643.
(14) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693−2698.
(15) Molander, G. A.; Etter, J. B. *Tetrahedron Lett.* **1984**, *25*, 3281−3284.
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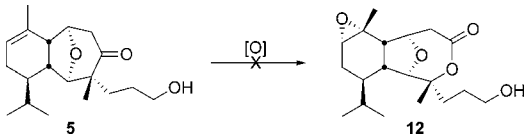
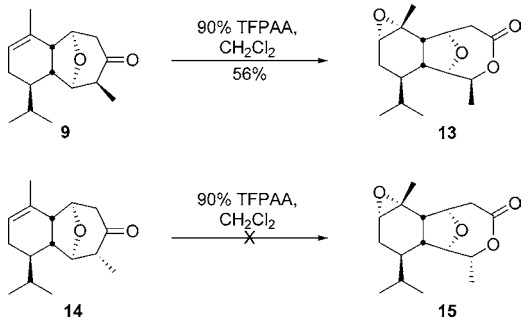
(22) Krapcho, A. P.; Glynn, G. A.; Grenon, B. J. *Tetrahedron Lett.* **1967**, 215−217.
(23) Jefford, C. W.; Sledeski, A. W.; Lelandais, P.; Boukouvalas, J. *Tetrahedron Lett.* **1992**, *33*, 1855−1858.
(24) Kabalka, G. W.; Yu, S.; Li, N.-S. *Tetrahedron Lett.* **1997**, *38*, 5455−5458.
(25) Kabalka, G. W.; Yu, S.; Li, N.-S. *Can. J. Chem.* **1998**, *76*, 800−805.

SCHEME 3. Baeyer−Villiger Oxidation Studies



SCHEME 4. Baeyer−Villiger Oxidation Studies



compound **5**. Several oxidizing agents were tried (*m*-CPBA, magnesium monoperoxyphthalate, trifluoroperacetic acid, peracetic acid, and bis(trimethylsilyl) peroxide) under a variety of conditions (changing the temperature, applying buffers and radical scavengers), but in all instances only epoxidation occurred and no traces of the Baeyer−Villiger oxidation product could be isolated (Scheme 3).[27]

Simultaneously, studies on model systems were also conducted (Scheme 4). Interestingly, applying trifluoroperacetic acid (TFPAA) generated from trifluoroacetic anhydride (TFAA) and 90% H_2O_2 on model ketone **9** led to the desired lactone **13**, while no lactone formation occurred on ketone **14**.[28]

These results may imply that the rate-determining step of this Baeyer−Villiger oxidation is the nucleophilic attack of the trifluoroperoxy acid to the ketone.[29,30] The outcome of the model studies could thus be explained by examining the three-dimensional structures of compounds **9** and **14** (Figure 2). In both cases, nucleophilic addition of trifluoroperacetic acid to the ketone is expected to occur from the less hindered convex face of the ring system. The 3D structures of compounds **9** and **14** reveal that in the case of compound **9**, where the methyl substituent is on the concave face, the attack of the peracid can take place without difficulty. However, when the methyl group is situated on the convex side of the ring system, as in compound **14**, the ketone is sterically encumbered, and thus the attack of the peracid is hindered (Figure 2).

The above findings prompted a revision of the synthetic strategy. The modified approach, shown in Scheme 5, diverged from the original synthesis after the [4 + 3] annulation. In this route, the allyl side chain was introduced onto the annulation product **6** directly. Subsequent functionalization would provide the required Baeyer−Villiger oxidation precursor **19**. As in the

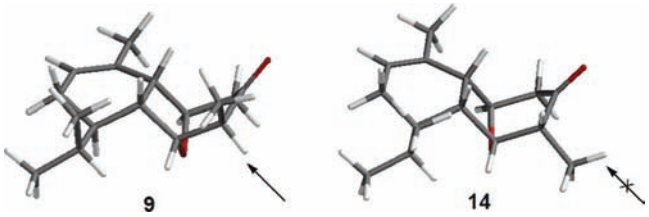
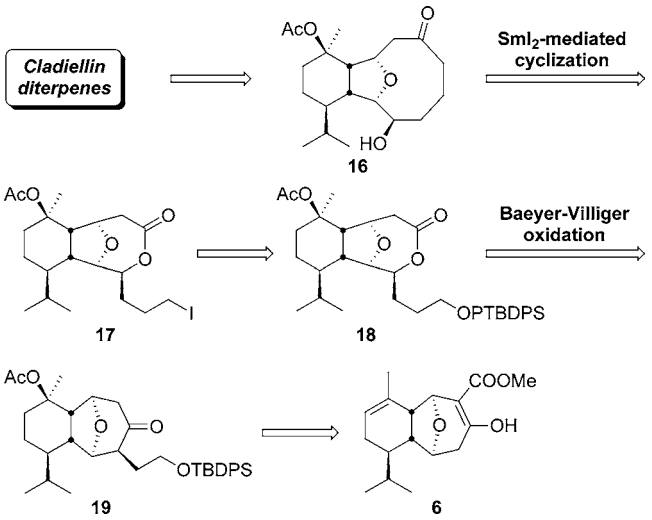
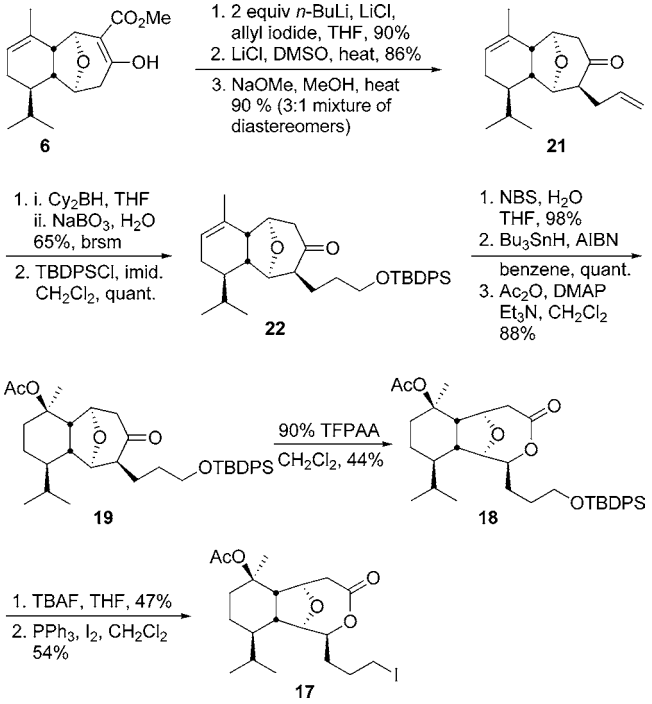


FIGURE 2. 3D representation of compounds **9** and **14**.

SCHEME 5. Second Synthetic Approach to the Cladiellin Skeleton



SCHEME 6. Synthesis of the SmI_2-Mediated Cyclization Precursor 17



previous approach, the construction of the oxacyclononane ring system was envisioned via a SmI_2-mediated acyl substitution.

The synthetic sequence investigating this approach is depicted in Scheme 6. The route started with the allylation of the [4 + 3] annulation product **6** using *n*-BuLi and allyl iodide, providing the product as the only diastereomer. Subsequent Krapcho decarboxylation and epimerization led to a 3:1 mixture of compound **21** and its epimer.[22] After separation, the minor

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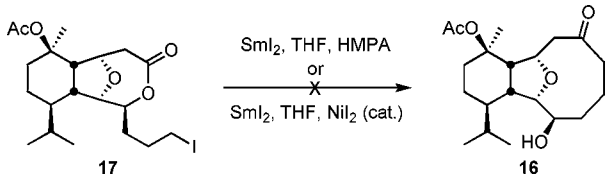
(27) Krow, G. R. *Org. React.* **1993**, *43*, 251−798.
(28) Cofre, P.; Sawyer, D. T. *Inorg. Chem.* **1986**, *25*, 2089−2092.
(29) Mosome, T.; Atarashi, S.; Muraoka, O. *Tetrahedron Lett.* **1974**, *42*, 3697−3700.
(30) Hunt, K. W.; Grieco, P. A. *Org. Lett.* **2000**, *2*, 1717−1719.

SCHEME 7. SmI_2-Mediated Reaction



diastereomer could be recycled and epimerized to the desired product. Selective hydroboration/oxidation could be achieved as before using dicyclohexylborane,[24,25] and the resulting alcohol was easily protected as a *tert*-butyldimethylsilyl ether.[31] Introduction of the tertiary acetate group was realized in a three-step sequence providing compound **19**. First, halohydrin formation was achieved using *N*-bromosuccinimide and water.[32] Removal of the bromide was accomplished in a radical reaction utilizing tributyltin hydride.[33,34] Subsequent acylation proved to be problematic due to the propensity of the tertiary alcohol to eliminate. After extensive optimization, it was found that this transformation could be effected using acetic anhydride, triethylamine, and substoichiometric quantities of DMAP, providing the Baeyer−Villiger oxidation precursor.[35] Gratifyingly, Baeyer−Villiger oxidation of compound **19** readily occurred using 90% trifluoroperacetic acid.[27] Further optimization of the oxidation was attempted using *m*-chloroperbenzoic acid, magnesium monoperoxyphthalate, and peracetic acid under various conditions, but trifluoroperacetic acid proved to be the most efficient oxidant. Subsequent formation of the cyclization precursor **17** was realized in two steps, first by removing the TBDPS protecting group using TBAF and forming the corresponding iodide by triphenylphosphine and iodine.[31,36]

With compound **17** in hand, the SmI_2-mediated acyl substitution was attempted in the presence of HMPA or NiI_2 (Scheme 7).[16,37] However, these transformations led only to reduced material, and no cyclization product could be observed.

The outcome of this reaction can be rationalized by unfavorable conformational effects. In the minimum energy conformation, the organosamarium side chain is in a quasi-equatorial orientation.[38] For the transformation to occur, this side chain must rotate into a quasi-axial orientation, and the attack on the lactone needs to occur from the concave face of the ring system (Figure 3). On the basis of MMFF calculations, the energy difference between the minimum energy conformation and the conformation where the side chain is in a quasi-axial orientation is 8.05 kcal/mol.

As the SmI_2-mediated acyl substitution did not lead to the desired product, a third approach was devised, which also included a SmI_2-mediated cyclization. However, the cyclization was planned to be performed on the more reactive and sterically more feasible iodo ketone **26** (Scheme 8). The cladiellin skeleton

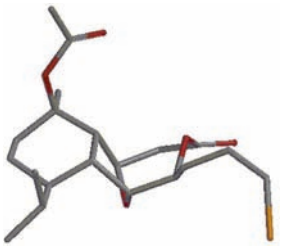
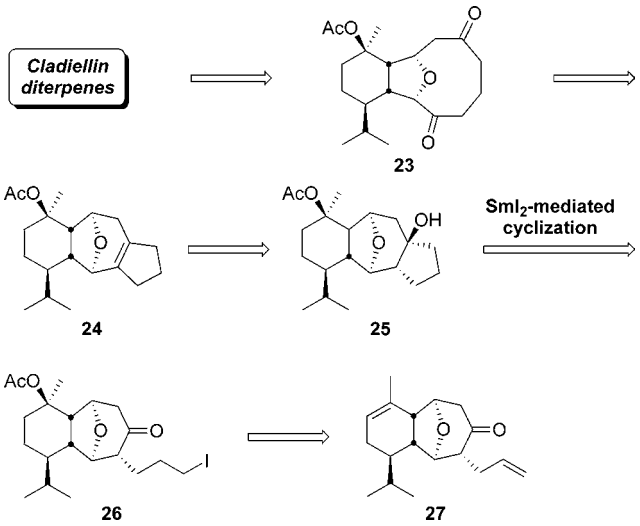


FIGURE 3. Minimum energy conformation of iodolactone **17**.

SCHEME 8. Third Synthetic Approach to the Cladiellin Skeleton



would then be obtained via elimination and oxidative cleavage of the resulting double bond.

To arrive at the cyclization precursor **26**, the sequence began with compound **27**, a known intermediate in the previous approach (Scheme 9). First, selective hydroboration of monosubstituted alkene was carried out with dicyclohexylborane.[24,25] To avoid protecting group manipulations, the primary alcohol was transformed into the corresponding alkyl chloride using hexachloroacetone and triphenylphosphine.[39] Introduction of the tertiary acetate could be achieved as before, in a three-step sequence.[32−35] To form the SmI_2-mediated cyclization precursor, the alkyl chloride was transformed to the corresponding alkyl iodide **26** via a Finkelstein reaction.[40] Gratifyingly, the key SmI_2-mediated Barbier reaction provided compound **25** in excellent yield.[15] Regioselective syn elimination of the tertiary alcohol could be effected using the Burgess reagent to give compound **24** as the only product in high yield.[41] Ozonolysis of the tetrasubstituted double bond provided the desired product **23**, a compound that incorporates all of the carbon atoms of the cladiellin skeleton.[42] With this transformation, the goal of constructing the cladiellin core was achieved.

Having synthesized the skeleton of the cladiellin natural products, the challenge to differentiate between the two carbonyl functionalities of compound **23** remained. Studies conducted on compound **23** indicated that a Wittig reaction, carried out

(31) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975−2977.
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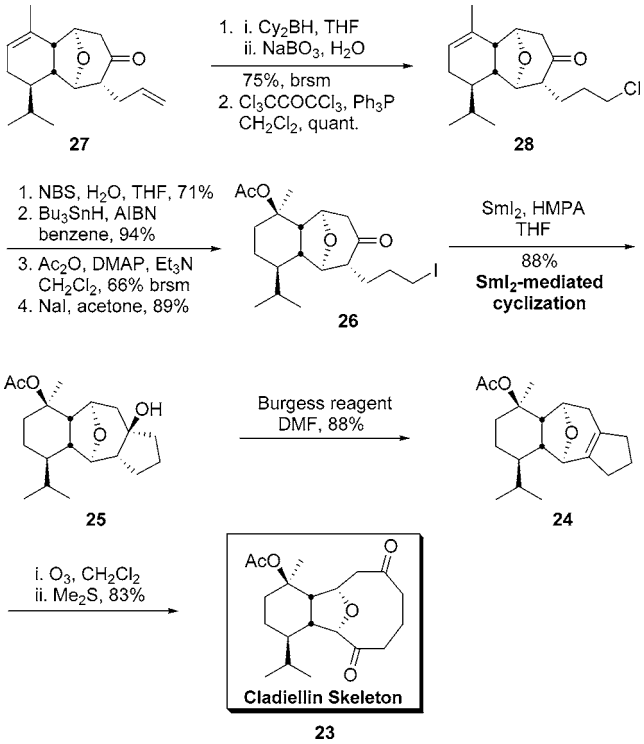
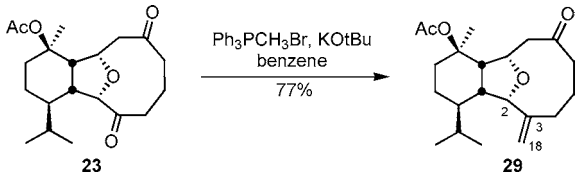
(38) *Spartan '04*, Molecular Mechanics Model, MMFF94 Forcefield, Conformation Distribution Calculation; Wavefunction, Inc.: Irvine, CA, 2004.
(39) Magid, R. M.; Fruchey, O. S.; Johnson, W. L. *Tetrahedron Lett.* **1977**, 2999−3002.
(40) Finkelstein, H. *Ber.* **1910**, *43*, 1528−1532.
(41) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 5224−5226.
(42) Bailey, P. S. *Chem. Rev.* **1958**, *58*, 925−1010.

SCHEME 9. Synthesis of the Cladiellin Skeleton



SCHEME 10. Chemoselective Wittig Reaction of Dicarbonyl 23



under carefully controlled conditions, occurs with very high selectivity at the C-3 carbonyl providing compound **29** (Scheme 10).[43] The structure of the product was unambiguously demonstrated by 2D-NMR experiments. The HMBC spectrum of molecule **29** shows a correlation between H-2 and C-3, H-2 and C-18, and H-18 and C-2 that clearly indicates the position of the double bond.

Several cladiellin natural products possess a tertiary alcohol at the C-7 position. Having compound **29** in hand, the formation of this functionality via methyl addition to the C-7 ketone was examined, devoting special attention to the diastereoselectivity of the transformation. On the basis of the crystal structure of diketone **23**, as well as the minimum energy conformation of keto alkene **29** (Figure 4),[13,44] addition was expected to occur from the more open convex face or "outside" of the ring system, providing the stereochemistry desired for several target structures.

Initial studies showed that methyl addition to the carbonyl could not be realized by methyllithium or methylmagnesium bromide. In these cases, only starting material was recovered, perhaps owing to enolization of the carbonyl. However, by using MeLi/Yb(OTf)$_3$ efficient carbonyl addition was effected.[45] Unfortunately, the stereochemistry of the resulting product could not be unambiguously proven by analysis of NOESY data of compound **30**. To elucidate the stereochemistry, the tertiary alcohol was transformed into compound **31** via oxymercuration with mercury trifluoroacetate and subsequent reduction (Scheme 11).[46]

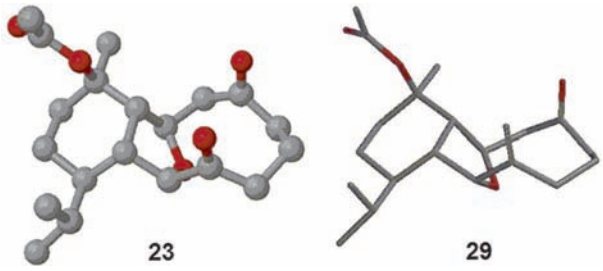


FIGURE 4. X-ray structure of diketone **23** and minimum energy conformation of keto alkene **29**.

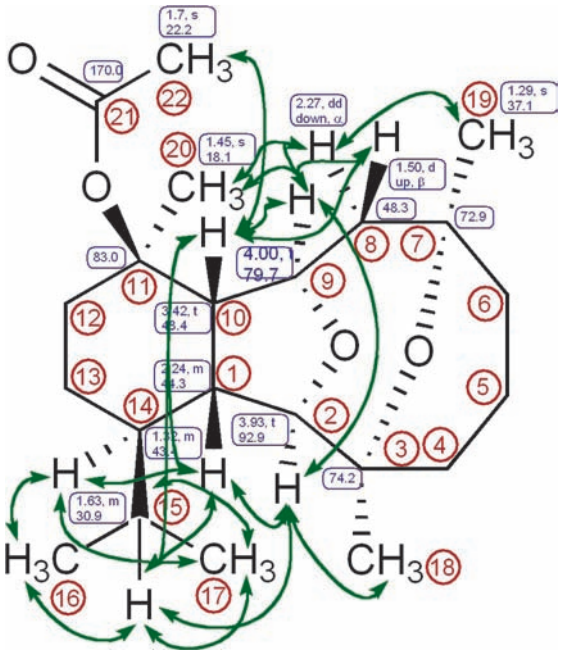


FIGURE 5. NOESY correlation of the 3,7-diastereomer of polyanthellin A.

The structure of the final product was established on the basis of 2D-NMR experiments. To our surprise, the unanticipated diastereomer was formed in high yield. Proton and carbon assignments were made based on COSY, HMQC, and HMBC experiments, and the stereochemistry was confirmed based on NOESY experiments. The characteristic correlation between H-2 and CH_3-18, and H-8α and CH_3-19, and the absence of correlations between H-1 and CH_3-18 and H-10 and CH_3-19 in the NOESY spectrum unambiguously established the stereochemistry of the product (Figure 5). These results indicated that methyl addition occurred from a conformation different than that predicted on the basis of the calculated and crystal structures, suggesting that, in the reactive conformation, chelation between the oxygen of the tetrahydrofuran ring and the ketone might play a key role. Unfortunately, addition of a polar, aprotic solvent such as HMPA to the MeLi/Yb(OTf)$_3$ reagent,

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(44) According to MMFF calculations, the energy difference between the minimum energy conformation and the conformation where the ketone is rotated out is 5.35 kcal/mol.
(45) Molander, G. A.; Burkhardt, E. R.; Weinig, P. *J. Org. Chem.* **1990**, *55*, 4990−4991.
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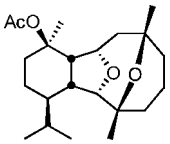
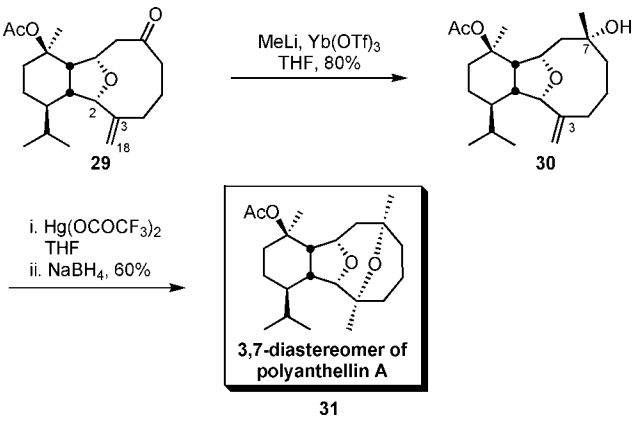


FIGURE 6. Polyanthellin A.

SCHEME 11. Synthesis of the 3,7-Diastereomer of Polyanthellin A



which would prevent chelate formation, again resulted in the recovery of starting material.

Compound **31** is the 3,7-diastereomer of a cladiellin natural product, polyanthellin A (Figure 6), which was isolated from the gorgonian *Briareum polyanthes* in 2002. The synthesis of this compound was achieved in only 17 overall steps without the use of protecting groups from commercially available (*R*)-(−)-α-phellandrene.

Conclusion

An efficient approach to the synthesis of the cladiellin skeleton was devised, featuring two methods that were previously developed in our research group. The medium-sized oxacyclononane subunit of the skeleton was created by a SmI_2-mediated cyclization.[15] The octahydroisobenzofuran moiety was synthesized via a [4 + 3]-annulation method.[13,17] Following this strategy, the cladiellin skeleton could be synthesized in only 14 steps without the use of protecting groups. This route also enabled the synthesis of the 3,7-diastereomer of polyanthellin A.

Experimental Section

Preparation of (1*R*,2*R*,3*R*,7*S*,8*R*,11*R*)-11-Allyl-10-hydroxy-3-isopropyl-6-methyl-12-oxatricyclo[6.3.1.0^{2,7}]dodeca-5,9-diene-9-carboxylic Acid, Methyl Ester (33). A flask containing LiCl (4.9 g, 116.4 mmol, 20 equiv) was flame-dried three times. After the salt was cooled to room temperature under an argon, a solution of compound **20** (1.7 g, 8.2 mmol) in THF (58 mL) was added. Subsequently, the solution was cooled to −78 °C, and *n*-BuLi (2.5 M in hexane, 5 mL, 12.5 mmol, 2.15 equiv) was added dropwise. The reaction was stirred at this temperature for 35 min. This process was followed by the dropwise addition of allyl iodide (793 μL, 8.7 mmol, 1.5 equiv). The reaction was allowed to warm to −50 °C and stirred for 40 min. The reaction was quenched with a saturated ammonium chloride solution (20 mL) at −50 °C. After warming to room temperature, the mixture was diluted with Et_2O and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with a concentrated NaCl solution and dried over $MgSO_4$, and the solvent was evaporated. The residue was purified via column chromatography applying EtOAc−hexane (3%) as eluent to provide compound **33** (1.75 g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.8 (s, 1H), 5.86 (m, 1H), 5.52 (s, 1H), 5.12 (d, *J* = 16.2 Hz, 1H), 5.11 (s, 1H), 4.66 (s, 1H), 3.93 (s, 1H), 3.52 (s, 3H), 2.58 (d, *J* = 14.1 Hz, 1H), 2.5 (d, *J* = 7.5 Hz, 1H), 2.36 (m, 1H), 2.29 (d, *J* = 7.1 Hz, 1H), 2.08 (dd, *J* = 9.8, 3.6 Hz, 1H), 2.0 (m, 2H) 1.73 (s, 3H), 1.43 (m, 1H), 1.38 (m, 1H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 170.3, 135.8, 133.9, 122.3, 117.2, 103.2, 81.5, 74.9, 51.5, 50.6, 47.0, 44.2, 42.3, 35.5, 29.0, 23.1, 21.5, 21.4, 21.0. IR (film): 3800−3000 (bs), 2955, 2867, 1658, 1618, 1442, 1363, 1305, 1260, 1248, 1203, 1147, 1081 cm^{-1}. $[\alpha]^{20}_D$ −78.9 (*c* 1.2, $CHCl_3$). HRMS calcd for $C_{20}H_{28}O_4$ [M + Na]$^+$ 355.1885, found 355.1879.

Preparation of (1*R*,2*R*,6*R*,7*R*,8*R*,9*R*)-9-Allyl-6-isopropyl-3-methyl-12-oxatricyclo[6.3.1.0^{2,7}] dodec-3-en-10-one (27). A round-bottom flask was charged with compound **33** (1.75 g, 5.27 mmol), LiCl (1.17 g, 26.3 mmol, 5 equiv), DMSO (100 mL), and H_2O (378 μL). The solution was warmed to 130 °C and stirred at this temperature for 4 h. After cooling the mixture to room temperature, a saturated NaCl solution (35 mL) was added. This mixture was extracted with Et_2O (5 × 20 mL). The combined organic phases were washed with a concentrated NaCl solution, dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure. The residue was purified via column chromatography applying EtOAc−hexane (3%) as eluent to provide compound **27** (1.24 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.74 (m, 1H), 5.54 (s, 1H), 5.09 (d, *J* = 15.1 Hz, 1H), 5.06 (d, *J* = 9.3 Hz, 1H), 4.46 (d, *J* = 5.1 Hz, 1H), 4.15 (s, 1H), 2.76 (dd, *J* = 15.0 5.1 Hz, 1H), 2.43 (m, 2H), 2.24 (series of multiplets, 3H), 2.15 (t, *J* = 6.5 Hz, 1H), 1.95 (d, *J* = 8.3 Hz, 1H), 1.55 (m, 1H), 1.66 (s, 3H), 1.60 (m, 1H), 1.32 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.9, 134.7, 132.3, 122.9, 117.4, 82.2, 78.6, 57.7, 47.6, 47.0, 45.1, 41.4, 35.2, 28.9, 22.4, 22.1, 21.5, 18.1. IR (film): 3070, 2956, 2868, 1712, 1442, 1385, 1184, 1036 cm^{-1}. $[\alpha]^{20}_D$ −156.0 (*c* 1.0, $CHCl_3$). HRMS calcd for $C_{18}H_{26}O_2^+$ [M]$^+$ 275.2011, found 275.1997.

Preparation of (1*R*,2*R*,6*R*,7*R*,8*R*,9*R*)-9-(3-Hydroxypropyl)-6-isopropyl-3-methyl-12-oxatricyclo[6.3.1.0^{2,7}]dodec-3-en-10-one (34). Compound **27** (770 mg, 2.81 mmol) was dissolved in THF (36 mL), and a solution of dicyclohexylborane (1 M in THF, 2.81 mL, 1 equiv) was added at room temperature under argon. The resulting solution was stirred for 30 min at room temperature. Subsequently, $NaBO_3 \cdot H_2O$ (1.29 g, 8.43 mmol, 3 equiv) and H_2O (10 mL) were added, and the reaction was stirred for an additional 4 h. Then the reaction mixture was diluted with Et_2O (10 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with a concentrated NaCl solution, dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure. The residue was purified via column chromatography applying EtOAc−hexane (20%) as eluent to provide compound **34** (618 mg, 75% based on recovered starting material). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.56 (s, 1H), 4.48 (d, *J* = 4.95 Hz, 1H), 4.15 (s, 1H), 3.65 (t, *J* = 5.5 Hz, 2H), 2.81 (dd, *J* = 15.0, 5.2 Hz, 1H), 2.42−2.20 (series of multiplets, 3H), 2.16 (t, *J* = 6.5 Hz, 1H), 1.95 (d, *J* = 15.0 Hz, 1H), 1.92−1.70 (series of multiplets, 4H), 1.68 (s, 3H), 1.68−1.51 (series of multiplets, 3H), 1.31 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.8, 132.3, 123.0, 83.5, 78.7, 62.2, 57.8, 47.4, 46.8, 45.2, 41.5, 29.9, 28.9, 27.4, 22.4, 22.1, 21.6, 18.1. IR (film): 3600−3100 (bs), 3070, 2956, 2868, 1711, 1446, 1385, 1366, 1187, 1146, 1064 cm^{-1}. $[\alpha]^{20}_D$ −107.7 (*c* 1.0, $CHCl_3$). HRMS calcd for $C_{18}H_{28}O_3$ [M + Na]$^+$ 315.1936, found 315.1928.

Preparation of (1*R*,2*R*,6*R*,7*R*,8*R*,9*R*)-9-(3-Chloropropyl)-6-isopropyl-3-methyl-12-oxatricyclo[6.3.1.0^{2,7}]dodec-3-en-10-one (28). To a solution of compound **27** (450 mg, 1.54 mmol) in CH_2Cl_2 (30 mL) was added Ph_3P (504 mg, 1.92 mmol, 1.25 equiv) under a nitrogen atmosphere at room temperature. The resulting

solution was cooled to −10 °C, and hexachloroacetone (373 μL, 2.46 mmol, 1.6 equiv) was added. The reaction was stirred at this temperature for 20 min. Then H_2O (10 mL) was added, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with saturated NaCl solution, dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure. The resulting residue was purified via column chromatography applying EtOAc−hexane (10%) as eluent to provide compound **28** (470 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.56 (d, *J* = 4.3 Hz, 1H), 4.48 (d, *J* = 5.0 Hz, 1H), 4.12 (s, 1H), 3.55 (m, 2H), 2.81 (dd, *J* = 15.0, 5.2 Hz, 1H), 2.35 (d, *J* = 6.2 Hz, 1H), 2.26 (d, *J* = 15.7 Hz, 1H), 2.24 (t, *J* = 6.2 Hz, 1H), 2.17 (t, *J* = 6.2 Hz, 1H), 1.97 (d, *J* = 15.7 Hz, 1H), 1.95−1.82 (series of multiplets, 3H), 1.82−1.72 (series of multiplets, 2H), 1.68 (s, 3H), 1.62 (dd, *J* = 15.0, 6.2 Hz, 1H), 1.31 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.1, 132.4, 123.0, 83.7, 78.8, 57.5, 47.4, 46.9, 45.2, 44.3, 41.6, 29.9, 29.0, 28.2, 22.4, 22.1, 21.6, 18.2. IR (film): 3070, 2954, 2933, 2894, 2864, 1705, 1409, 1379, 1292, 1191, 1128, 1104, 1083 cm^{-1}. $[\alpha]^{20}_D$ −108.5 (*c* 0.55, $CHCl_3$). HRMS calcd for $C_{18}H_{27}ClO_2$ $[M]^+$ 333.1597, found 333.1589.

Preparation of (1*R*,2*R*,3*S*,4*S*,6*R*,7*R*,8*R*,9*R*)-4-Bromo-9-(3-chloropropyl)-3-hydroxy-6-isopropyl-3-methyl-12-oxatricyclo-[6.3.1.0^{2,7}]dodecan-10-one (39). Compound **28** (450 mg, 1.45 mmol) was dissolved in a mixture of THF (17.4 mL) and H_2O (3.2 mL). To this solution was added NBS (334 mg, 1.89 mmol, 1.3 equiv) in three portions over 1 h at 0 °C under nitrogen. The reaction was allowed to warm to room temperature and stirred for 4 h. Then the mixture was diluted with H_2O (3 mL) and Et_2O (5 mL) The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic phases were washed with a saturated NaCl solution, dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure. The resulting residue was purified via column chromatography applying EtOAc−hexane (20%) as eluent to provide compound **39** (450 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.81 (d, *J* = 4.5 Hz, 1H), 4.11 (m, 2H), 3.53 (t, *J* = 6.1 Hz, 2H), 2.81 (dd, *J* = 15.5, 5.0 Hz, 1H), 2.27 (d, *J* = 15.5 Hz, 1H), 2.12−2.07 (series of multiplets, 5H), 2.0 (m, 1H), 1.9−1.6 (m, 6H), 1.41 (s, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.5, 84.2, 77.5, 72.3, 62.8, 57.0, 53.2, 47.8, 44.9, 44.2, 39.7, 30.9, 30.3, 29.7, 28.3, 21.8, 21.2, 15.7. IR (film): 3600−3100, 2957, 2873, 1710, 1453, 1434, 1410, 1371, 1349, 1229, 1171, 1123, 1037 cm^{-1}. $[\alpha]^{20}_D$ +20.3 (*c* 1.5, $CHCl_3$). HRMS calcd for $C_{18}H_{28}BrClO_3$ $[M]^+$ 429.0808, found 429.0824.

Preparation of (1*R*,2*R*,3*S*,6*R*,7*R*,8*R*,9*R*)-9-(3-Chloropropyl)-3-hydroxy-6-isopropyl-3-methyl-12-oxatricyclo[6.3.1.0^{2,7}]dodecan-10-one (40). To a solution of compound **39** (450 mg, 1.10 mmol) and AIBN 18 mg, 0.11 mmol) in benzene (11 mL) was added *n*-Bu_3SnH (355 μL, 1.32 mmol, 1.2 equiv) under an argon atmosphere. The reaction was warmed to 90 °C and stirred at this temperature for 1 h. Subsequently, the reaction was cooled to room temperature, and the solvent was removed under reduced pressure. The resulting residue was purified via column chromatography applying EtOAc−hexane (20%) as eluent to provide compound **40** (360 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.31 (bs, 1H), 4.01 (s, 1H), 3.53 (m, 2H), 1.77 (dd, *J* = 15, 4.3 Hz, 1H), 2.31 (d, *J* = 15 Hz, 1H), 2.15 (t, *J* = 6.7 Hz, 1H), 2.08 (dd, *J* = 10.0, 8.0 Hz, 1H), 1.97 (m, 1H), 1.88−1.73 (series of multiplets, 3H), 1.66 (m, 1H), 1.62 (s, 1H), 1.56 (m, 1H), 1.47−1.25 (series of multiplets, 4H), 1.24 (s, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 1H), 0.82 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.2, 84.7, 76.5, 70.3, 55.3, 55.2, 50.1, 46.5, 44.8, 42.3, 35.4, 31.0, 30.3, 29.7, 29.6, 22.0, 18.4, 17.1. IR (film): 3600−3100, 2956, 2870, 1709, 1463, 1410, 1396, 1287, 1196, 1075 cm^{-1}. $[\alpha]^{20}_D$ −6.93 (*c* 1.6, $CHCl_3$). HRMS calcd for $C_{18}H_{29}ClO_3-H_2O$ $[M - H_2O]^+$ 310.1699, found 310.1695.

Preparation of (1*R*,2*R*,3*S*,6*R*,7*R*,8*R*,9*R*)-Acetic Acid 9-(3-Chloropropyl)-6-isopropyl-3-methyl-10-oxo-12-oxatricyclo-[6.3.1.0^{2,7}]dodec-3-yl Ester (41). To a solution of compound **40** (113 mg, 0.34 mmol) in CH_2Cl_2 (3.4 mL) was added Et_3N (143 μL, 1.03 mmol, 3 equiv), Ac_2O (100 μL, 1.05 mmol, 3.05 equiv), and DMAP (17 mg, 0.14 mmol, 0.4 equiv). The reaction was stirred at room temperature for 6 h. Addition of Et_3N and Ac_2O was repeated twice. Then the reaction was cooled to −10 °C and stirred overnight at this temperature. Upon completion of the reaction, H_2O (5 mL) was added, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic phases were washed with saturated NaCl solution and dried ($MgSO_4$). The solvent was evaporated under reduced pressure. The resulting residue was purified via column chromatography applying EtOAc−hexane (10%) as eluent to provide compound **41** (65 mg, 66% BRSM). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.34 (bs, 1H), 3.99 (s, 1H), 3.54 (m, 2H), 2.78 (dd, *J* = 15.0, 4.3 Hz, 1H), 2.39 (d, *J* = 13.0 Hz, 1H), 2.33 (d, *J* = 15.5 Hz, 1H), 2.26 (m, 1H), 2.16 (m, 1H), 2.06 (dd, *J* = 10.0, 8.0 Hz 1H), 1.95 (s, 3H), 1.90−1.72 (m, 4H), 1.64 (m, 1H), 1.5 (s, 3H), 1.45 (m, 1H), 1.40−1.20 (series of multiplets, 2H), 1.13 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.6, 169.9, 84.8, 82.2, 75.3, 54.6, 52.9, 49.6, 46.0, 44.3, 42.0, 30.8, 30.5, 29.8, 29.3, 23.9, 22.3, 21.3, 18.3, 16.6. IR (film): 2956, 2872, 1728, 1712, 1462, 1443, 1366, 1258, 1190, 1145, 1119 cm^{-1}. $[\alpha]^{20}_D$ −13.4 (*c* 0.7, $CHCl_3$). HRMS calcd for $C_{20}H_{31}ClO_4$ $[M + Na]^+$ 393.1808, found 393.1824.

Preparation of (1*R*,2*R*,3*S*,6*R*,7*R*,8*R*,9*R*)-Acetic Acid 9-(3-Iodopropyl)-6-isopropyl-3-methyl-10-oxo-12-oxatricyclo[6.3.1.0^{2,7}]-dodec-3-yl Ester (26). To a solution of compound **41** (75 mg, 0.20 mmol) in acetone (2 mL) was added sodium iodide (304 mg, 2.02 mmol, 10 equiv). The reaction was warmed to 57 °C and stirred for 14 h under nitrogen at this temperature. Upon completion, the reaction was cooled to room temperature, and the solvent was removed under reduced pressure. The resulting residue was purified via column chromatography applying EtOAc−hexane (10%) as eluent to provide compound **26** (83 mg, 89% BRSM).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.35 (bs, 1H), 3.98 (s, 1H), 3.18 (t, *J* = 6.25 Hz, 2H), 2.79 (dd, *J* = 15.0, 3.5 Hz, 1H), 2.40 (d, *J* = 13 Hz, 1H), 2.34 (d, *J* = 15.5 Hz, 1H), 2.27 (d, *J* = 4.45 Hz, 1H), 2.16 (m, 1H), 2.06 (dd, *J* = 10.25, 8.0 Hz, 1H), 1.95 (s, 3H), 1.90−1.78 (series of multiplets, 3H), 1.65 (m, 1H), 1.59 (m, 1H), 1.51 (s, 3H), 1.56 (m, 1H), 1.39−1.25 (series of multiplets, 2H), 1.14 (dt, *J* = 15.6, 3.5 Hz, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.5, 169.9, 84.8, 82.2, 75.3, 54.4, 52.9, 49.6, 46.0, 44.3, 42.0, 32.8, 30.8, 30.5, 23.9, 22.3, 21.3, 18.3, 16.6, 5.7. IR (film): 2955, 2872, 1728, 1711, 1462, 1442, 1366, 1257, 1191, 1118 cm^{-1} $[\alpha]^{20}_D$ −14.5 (*c* 0.4, $CHCl_3$). HRMS calcd for $C_{20}H_{31}IO_4$ $[M + Na]^+$ 485.1164, found 485.1154.

Preparation of Tetracyclic Quaternary Alcohol 25. Preparation of the SmI_2 solution: To a slurry of Sm (59 mg, 0.39 mmol, 3.6 equiv) in THF (2.4 mL) was added CH_2I_2 (26 μL, 0.33 mmol, 3 equiv) in two portions, dropwise, under an argon atmosphere at room temperature. The solution was stirred for 4 h. Then the solution was cooled to 0 °C, and HMPA (420 μL, 1.98 mmol, 18 equiv) was added. The solution was then stirred for 15 min at 0 °C. Procedure for the SmI_2-mediated cyclization: A solution of compound **26** (52 mg, 0.11 mmol) in THF (1.1 mL) was added dropwise via cannula to the SmI_2 solution. The reaction was allowed to warm to room temperature and stirred for 1 h. Upon completion, the reaction was quenched with Rochelle's salt solution (1 mL), and the mixture was stirred at room temperature for 20 min. This was followed by the addition of H_2O (2 mL) and Et_2O (3 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 1.5 mL). The combined organic phases were washed with a saturated NaCl solution, dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure. The resulting residue was purified via column chromatography applying EtOAc−hexane (20%) as eluent to provide compound **25** (32 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.09 (bs, 1H), 3.78 (s, 1H), 3.27

(d, J = 8.4, 1H), 2.25−2.13 (series of multiplets, 2H), 2.08−1.97 (series of multiplets, 2H), 1.97 (s, 3H), 1.80−1.56 (series of multiplets, 9H), 1.54 (s, 3H), 1.52−1.38 (series of multiplets, 2H), 1.30−1.12 (series of multiplets, 2H), 0.92 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 70.3, 83.8, 83.5, 77.5, 74.7, 50.1, 48.8, 46.3, 45.0, 44.5, 42.0, 31.3, 31.2, 30.9, 23.7, 22.6, 22.5, 21.4, 18.5, 16.5. IR (film): 3600−3100 (bs), 2952, 2871, 1728, 1442, 1383, 1252, 1148 cm^{-1}. $[\alpha]^{20}_D$ +40.5 (*c* 0.2, $CHCl_3$). HRMS calcd for $C_{20}H_{32}O_4$ $[M]^+$ 359.2198, found 359.2196.

Preparation of Tetracyclic Alkene 24. To a solution of compound **25** (55 mg, 0.164 mmol) in MeCN (1.6 mL) was added the Burgess reagent[3] (86 mg, 0.36 mmol, 2.2 equiv) under a nitrogen atmosphere. The solution was warmed to 70 °C and stirred for 40 min. Upon completion, the reaction mixture was allowed to cool to room temperature, and H_2O (1 mL) was added. The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 0.5 mL). The combined organic phases were washed with a saturated NaCl solution, dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure. The resulting residue was purified via column chromatography applying Et_2O−hexane (10%) solvent system as eluent to provide compound **24** (45 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.14 (bs, 1H), 4.10 (s, 1H), 2.59 (d, J = 16.5 Hz, 1H), 2.46 (m, 1H), 2.40 (d, J = 14 Hz, 1H), 2.35−2.25 (series of multiplets, 3H), 2.21 (m, 1H), 2.12 (t, J = 8.5, 1H), 1.97 (s, 3H), 1.88 (series of multiplets, 2H), 1.74 (d, J = 16.5 Hz, 1H), 1.66 (m, 1H), 1.55 (s, 3H), 1.48−1.32 (series of multiplets, 2H), 1.27 (t, J = 13 Hz, 1H), 1.12 (t, J = 13 Hz, 1H), 0.95 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 137.8, 131.5, 83.4, 80.4, 74.5, 53.2, 48.2, 41.8, 36.2, 34.9, 32.3, 31.2, 30.7, 24.6, 22.4, 22.2, 21.3, 19.0, 17.0. IR (film): 2956, 2872, 1725, 1442, 1366, 1247, 1185, 1143, 1040 cm^{-1}. $[\alpha]^{20}_D$ −8.66 (*c* 0.3, $CHCl_3$). HRMS calcd for $C_{20}H_{30}O_3$ $[M]^+$ 318.2194, found 318.2190.

Preparation of (1*R*,2*S*,3*R*,6*R*,7*R*,8*R*)-Acetic Acid 6-Isopropyl-3-methyl-9,13-dioxo-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-3-yl Ester (23). A solution of compound **24** (45 mg, 0.14 mmol) in CH_2Cl_2 (1.4 mL) was cooled to −78 °C, and O_3 was bubbled through the solution until a faint blue color persisted (approximately 10 s). The solution was purged with argon at −78 °C for 10 min to remove excess O_3, and then Me_2S (100 μL) was added. The reaction was stirred overnight at room temperature. The solvent was evaporated under reduced pressure, and the resulting residue was purified via column chromatography applying EtOAc−hexane (30%) solvent system as eluent to provide compound **23** (40 mg, 83%). ^{1}H NMR (500 MHz, C_6D_6): δ 3.90 (dd, J = 9.5, 6.5 Hz, 1H), 3.83 (s, 1H), 2.96 (dd, J = 12.0, 5.5 Hz, 1H), 2.87 (dd, J = 11.5, 6.5 Hz 1H), 2.8 (dd, J = 5.5, 2.5 Hz, 1H), 2.69 (d, J = 14.5 Hz, 1H), 2.59 (t, J = 6.5, 2.5 Hz, 1H), 2.47 (t, J = 6.5 Hz, 1H), 2.21 (q, J = 14 Hz, 1H), 2.06 (d, J = 11.5 Hz, 1H), 2.00−1.85 (series of multiplets, 2H), 1.59 (s, 3H), 1.55−1.45 (m, 1H), 1.27−1.03 (series of multiplets, 3H), 0.98 (m, 1H), 0.80 (t, J = 6.5 Hz, 1H), 0.81 (d, J = 6.5 Hz, 3H), 0.74, (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6): δ 210.7, 210.1, 169.4, 88.4, 81.2, 78.4, 48.2, 48.0, 44.1, 40.3, 40.2, 39.5, 31.8, 30.0, 28.8, 24.5, 23.1, 21.7, 18.8, 15.5. IR (film): 2956, 2872, 1725, 1442, 1367, 1241, 1185, 1143, 1072, 1017 cm^{-1}. $[\alpha]^{20}_D$ +50 (*c* 0.15, $CHCl_3$). HRMS calcd for $C_{20}H_{30}O_4$ $[M + Na]^+$ 373.1990, found: 373.1992.

Preparation of (1*R*,2*S*,3*R*,6*R*,7*R*,8*R*)-Acetic Acid 6-Isopropyl-3-methyl-9-methylene-13-oxo-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-3-yl Ester (29). Procedure for the preparation of the phosphorus ylide: To a solution of Ph_3PCH_3Br (214 mg, 0.625 mmol) in benzene (5 mL) was added KO*t*-Bu (56 mg, 0.5 mmol). The mixture was stirred at 40 °C for 30 min.

Procedure for the Wittig reaction: Compound **23** (21 mg, 0.06 mmol) was dissolved in benzene (600 μL), and the stock solution of the ylide (700 μL, 0.625 mmol, 1.1 equiv) was added under an argon atmosphere. The reaction was warmed to 80 °C and was stirred for 30 min. The addition of the stock solution was repeated. The reaction was monitored by thin-layer chromatography. Upon consumption of the starting material, the reaction was quenched with a saturated NaCl solution (1 mL). The phases were separated, and the aqueous phase was extracted with benzene (2 × 0.5 mL) and EtOAc (2 × 0.5 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The resulting residue was purified via column chromatography applying Et_2O−hexane (10%) solvent system as eluent to provide compound **29** (16 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.96 (s, 1H), 4.90 (s, 1H), 4.25 (s, 1H), 5.15 (t, J = 6.5 Hz, 1H), 3.25 (dd, J = 11.5, 6.0 Hz, 1H), 2.85−2.75 (series of multiplets, 2H), 2.63 (d, J = 14 Hz, 1H), 2.39 (dd, J = 11.5, 6.5 Hz, 1H), 2.34 (d, J = 11.5 Hz, 1H), 2.30−2.15 (series of multiplets, 2H), 2.20−2.05 (series of multiplets, 2H) 2.00, (s, 3H), 1.75 (m, 1H), 1.50 (s, 3H), 1.48 (m, 1H), 1.39−1.08 (series of multiplets, 4H), 0.94 (d, J = 6.5 Hz, 3H), 0.78 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.5, 169.9, 148.4, 113.7, 85.2, 82.4, 76.7, 48.5, 48.3, 44.4, 42.1, 40.7, 34.1, 29.7, 28.7, 26.0, 24.4, 22.4, 21.6, 18.5, 15.6. IR (film): 2956, 2929, 2872, 1729, 1705, 1367, 1245, 1144, 1045, 1020 cm^{-1} $[\alpha]^{20}_D$ +7.0 (*c* 0.1, $CHCl_3$). HRMS calcd for $C_{21}H_{32}O_4$ $[M]^+$ 348.2300, found 348.2298.

Preparation of (1*R*,2*S*,3*R*,6*R*,7*R*,8*R*,13*R*)-Acetic Acid 13-Hydroxy-6-isopropyl-3,13-dimethyl-9-methylene-15-oxatricyclo-[6.6.1.0^{2,7}]pentadec-3-yl Ester (30). Procedure for the preparation of the $Yb(OTf)_3$·MeLi solution: $Yb(OTf)_3$ (285 mg, 0.46 mmol) was dissolved in THF (4.6 mL) under an argon atmosphere. The slurry was stirred for 15 min at room temperature, and then it was cooled to −78 °C. This was followed by the addition of MeLi (1 M in hexane, 460 μL, 0.46 mmol), and the resulting deep red solution was stirred at this temperature for 30 min.

Procedure for methyl addition to carbonyl: Compound **29** (11 mg, 0.031 mmol) was dissolved in THF (310 μL), and the resulting solution was cooled to −78 °C under an argon atmosphere. To this mixture an excess of the $Yb(OTf)_3$·MeLi stock solution was added until a faint red color persisted. The reaction was followed by thin-layer chromatography. Upon consumption of the starting material, the reaction was queched at −78 °C with saturated $NaHCO_3$ (400 μL). The mixture was allowed to warm to room temperature and was diluted with diethyl ether (500 μL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 200 μL). The combined organic phases were washed with a saturated NaCl solution, dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure. The resulting residue was purified via column chromatography applying Et_2O−hexane (10%) solvent system as eluent to provide compound **30** (9 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.93 (s, 1H), 4.87 (s, 1H), 4.14 (s, 1H), 4.04 (m, 1H), 2.63 (t, J = 5.5 Hz, 1H), 2.46−2.35 (series of multiplets, 3H), 2.29 (dd, J = 8.0, 5.5 Hz, 1H), 2.00 (s, 3H), 1.99 (m, 1H), 1.85 (dd, J = 14.5, 11.0 Hz, 1H), 1.77−1.71 (series of multiplets, 2H), 1.53 (m, 1H), 1.46 (s, 3H), 1.43 (m, 1H), 1.30−1.23 (series of multiplets, 4H), 1.20 (m, 1H), 1.13 (s, 3H), 0.94 (d, J = 7 Hz, 3H), 0.88 (t, J = 7 Hz, 1H), 0.82 (d, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 152.3, 110.9, 85.3, 82.6, 76.1, 73.1, 53.8, 47.3, 43.5, 41.4, 41.06, 37.6, 31.3, 30.8, 29.6, 26.8, 24.2, 22.5, 21.6, 18.3, 16.2. IR (film): 3650−3000, 2951, 2914, 2851, 1727, 1470, 1375, 1250, 1080 cm^{-1}. $[\alpha]^{20}_D$ +52.0 (*c* 0.1, $CHCl_3$). HRMS calcd for $C_{21}H_{36}O_4$ $[M + Na]^+$ 387.2511, found 387.2498.

Preparation of 3,7-Diastereomer of Polyanthellin A (31). To a solution of compound **30** (2.8 mg, 0.0077 mmol) in THF (300 μL) was added a solution of $Hg(OCOCF_3)$ (6.5 mg, 0.0153 mmol, 2 equiv) in THF (300 μL) under an argon atmosphere. The reaction mixture was warmed to 55 °C and stirred at this temperature for 3 h. Subsequently, the reaction was cooled to room temperature, and $NaBH_4$ (3.5 mg, 0.092 mmol, 12 equiv) was added. The reaction was stirred for 30 min. Then it was quenched with saturated $NaHCO_3$ solution (500 μL), and the mixture was diluted with Et_2O (600 μL). The phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 200 μL). The combined organic phases were washed with a saturated NaCl solution, dried ($MgSO_4$),

and filtered. The solvent was removed under reduced pressure. The resulting residue was purified via column chromatography applying Et_2O−hexane (10%) solvent system as eluent to provide the 3,7-diastereomer of polyanthellin A (1.6 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.046 (t, J = 5.5 Hz, 1H), 3.74 (s, 1H), 3.26 (t, J = 5.5 Hz, 1H), 2.24 (dd, J = 14.0, 5.5 Hz, 1H), 2.17−2.13 (series of multiplets, 2H), 2.00 (s, 3H), 1.85 (m, 1H), 1.69−1.54 (series of multiplets, 6H), 1.49 (s, 3H), 1.46−1.35 (series of multiplets, 3H), 1.25 (s, 6H), 1.32−1.2 (series of multiplets, 2H), 0.94 (d, J = 7 Hz, 3H), 0.82 (d, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 152.3, 110.9, 85.3, 82.6, 76.1, 73.1, 53.8, 47.3, 43.5, 41.4, 41.0, 37.6, 31.3, 30.8, 29.6, 26.8, 24.2, 22.5, 21.6, 18.3, 16.2. IR (film): 2951, 2914, 2851, 1727, 1462, 1443, 1257, 1076, 1013, 796 cm^{-1}. $[\alpha]^{20}_D$ +47.5 (*c* 0.05, $CHCl_3$). HRMS calcd for $C_{22}H_{36}O_4$ $[M + H]^+$ 365.2676, found 365.2685.

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Supporting Information Available: Experimental details and structural data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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