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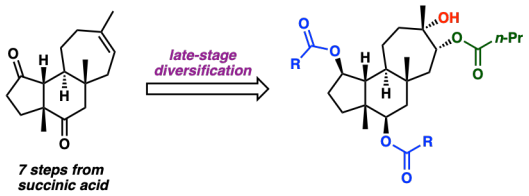

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Synthesis of non-natural cyanthiwigin–gagunin hybrids through late-stage diversification of the cyanthiwigin natural product core

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ABSTRACT

Derivitization of natural product scaffolds produces diversely functionalized molecules for biological study and offers insight into the reactivities of complex molecular architectures. In the present study, the tricyclic framework of the cyanthiwigin natural product family was employed as a platform for late-stage diversification. The design and synthesis of several non-natural "hybrid" molecules resembling both the cyanthiwigin and gagunin natural products was accomplished, and the results of these investigations are described herein.

1. Introduction

Natural products have long served as important targets for total synthesis, attracting attention with their intriguing biological activities and impressive molecular architectures.[1] Synthetic efforts toward natural products frequently inspire diversification studies due to ready availability of complex late-stage intermediates.[2,3] Generally embodying the main carbon frameworks of the associated natural product families, these scaffolds serve as ideal platforms for diversification. They enable access to complex derivatives unattainable through operational biosynthetic pathways[2] and can be more accessible than the natural products themselves (for instance, due to low-yielding endgame transformations toward the latter).[4,5] Furthermore, diversification of a natural product scaffold can generate an array of complex molecules while also revealing important reactivity patterns of the molecular framework.[3,6]

Related natural product families often feature similar carbon skeletons while exhibiting varied biological activities.[6a] Derivitization of the common framework produces "hybrid" molecules incorporating salient features (e.g. oxidation states, substitution patterns, functional groups) of the parent families that could exhibit heightened potency or even novel activity.[4,7] This strategy was employed to good effect by the Paterson group in their preparation of discodermolide–dictyostatin hybrids which displayed greater potency than the parent compounds against pancreatic, colon, and ovarian cancer cell lines.[8] Inspired by these efforts, we sought to create hybrid compounds resembling another pair of bioactive marine natural product families, the cyanthiwigins and the gagunins.

Comprising a subset of a large class of bioactive natural products known as the cyathins, the cyanthiwigin diterpenoids were first isolated from the marine sponge *Epipolasis reiswigi* in 1992,[9] with more compounds extracted from *Myrmekioderma styx* a decade later.[10] With the exception of cyanthiwigin AC, the cyanthiwigins possess 5–6–7 fused tricyclic carbon skeletons (**1**) featuring four contiguous stereocenters, two of which are quaternary. Additionally, many of these compounds display noteworthy biological activity against such disease agents as HIV-1 (cyanthiwigin B, **2**), lung cancer and leukemia cells (cyanthiwigin C, **3**), and primary tumor cells (cyanthiwigin F, **4**) (Figure 1).

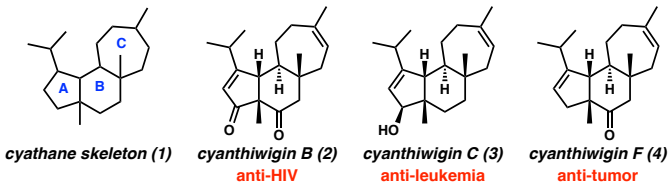


Figure 1. The cyathane skeleton and selected cyanthiwigins.

Since not all of the cyanthiwigins have been isolated in large enough quantities for biological evaluation, exhaustive exploration of the medicinal properties of all thirty known cyanthiwigins has remained elusive. Noting this limitation along with the structural challenges presented by the molecules, chemists have targeted various members of the cyanthiwigin family for total synthesis.[11,12] To date, ten cyanthiwigins have been prepared, including cyanthiwigins U, W, and Z by Phillips and co-workers;[13] cyanthiwigin AC by Reddy and co-workers;[14]

cyanthiwigins B, F, and G by Stoltz and co-workers;[15] and cyanthiwigins A, C, G, and H by Gao and co-workers.[16]

Featuring the same 5–6–7 tricyclic core as the cyanthiwigins, the structurally related gagunin diterpenoids were isolated from the sponge *Phorbas* sp. by Shin and co-workers off the coast of South Korea and exhibit varying biological activities.[17] An important structural difference between the gagunins and the cyanthiwigins is the degree of oxidation surrounding the carbocyclic core. The density of functionalization and presence of numerous contiguous stereocenters (up to 11) render the gagunins challenging targets for total synthesis, and as such, only partial syntheses of the gagunins have been completed to date.[18]

The gagunins exhibit cytotoxic activity against the human leukemia cell line K562, with gagunin E (**5**) displaying the most potent activity (LC_{50} = 0.03 μg/mL) out of all 17 known members of the natural product family. Gagunin E (**5**) is over one thousand times more potent than the least biologically active member of the family, gagunin A (**6**) (Figure 2). Interestingly, these two compounds differ only in the placement and identity of the ester substituents surrounding the carbocyclic framework, an observation that led Shin and co-workers to hypothesize that the biological properties of the gagunins are highly sensitive to the ester functionalities, especially at the C11 position. Indeed, evaluation of perhydroxylated gagunin A (**7**), in which all of the esters are hydrolyzed, revealed no appreciable biological activity, lending credence to Shin's hypothesis.

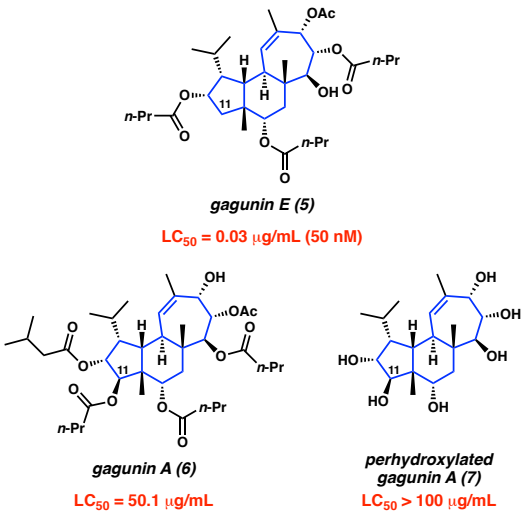
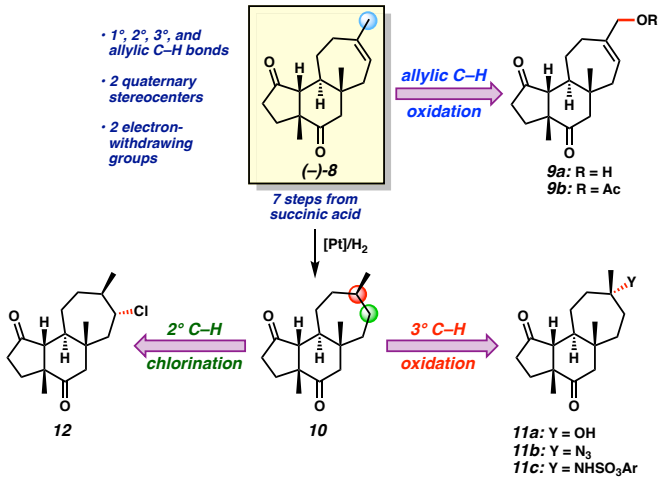


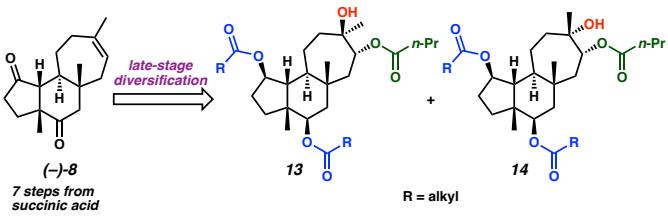
Figure 2. Structures and anti-leukemia activities of selected gagunins.

With this in mind, we envisioned that tricycle **8** could serve as a platform for accessing non-natural compounds resembling both the cyanthiwigin and gagunin natural products. Available in 7 steps from succinic acid via a double enantioselective decarboxylative allylic alkylation strategy,[15,19] compound (–)-**8** had previously been employed in a comparative study of late-stage C–H functionalization (Scheme 1).[20] Along with allylic C–H oxidation of **8**, various methods for 2° C–H chlorination and 3° C–H hydroxylation, amination, and azidation of hydrogenated tricycle **10** were compared. These efforts revealed reactivity patterns of the cyanthiwigin core and identified robust protocols for C–H oxidation of complex molecules.

For the present study, we anticipated that the two carbonyls and C-ring olefin in **8** could serve as functional handles for facile installation of ester functionalities, generating poly-esterified compounds (**13**–**14**) reminiscent of the densely oxygenated gagunins (Scheme 2). Given the diverse biological activities displayed by the parent cyanthiwigins and gagunins, we hypothesized that some of these cyanthiwigin–gagunin "hybrid" molecules might exhibit interesting biological properties that could be correlated to structure through systematic fine-tuning of the ester substituents. Overall, these efforts could identify exceptionally potent complex molecules[7] while providing insight into the reactivity of the cyanthiwigin core and the relationship between framework substitution and biological activity.



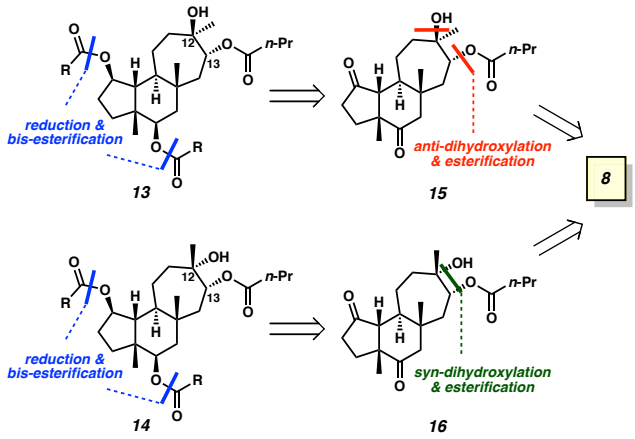
Scheme 1. Previous work using the cyanthiwigin scaffold (**8**) in a comparative study of late-stage C–H oxidation.



Scheme 2. Approach toward cyanthiwigin–gagunin hybrid synthesis.

2. Results and Discussion

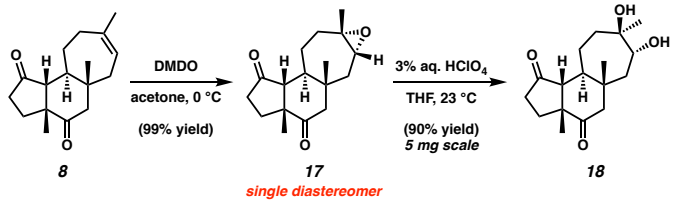
At the outset, we identified the C-ring olefin in **8** as a key starting point for diversification. Oxygenation could be achieved through di-hydroxylation of the olefin with either *anti* or *syn* relative stereochemistry, giving rise to cyanthiwigin–gagunin hybrids diastereomeric at C12 and C13. Retrosynthetically, hybrids **13** and **14** could arise through reduction and bis-esterification of diketones **15** or **16**, respectively. These intermediates would be accessed through either *anti*- or *syn*-dihydroxylation of **8**, followed by esterification (Scheme 3).



Scheme 3. Retrosynthetic analysis of hybrids **13**–**14**.

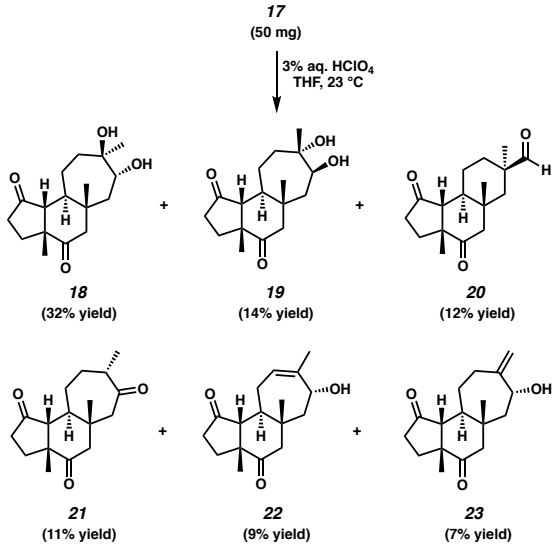
2.1. Anti diol route

We began our studies targeting hybrid molecules (**13**) derived from the *anti*-dihydroxylation pathway. We envisioned that the *anti*-diol moiety could be installed in the C-ring by way of olefin epoxidation and subsequent ring-opening. To this end, we treated tricycle **8** with DMDO at 0 °C, forming epoxide **17** in excellent yield as a single diastereomer (Scheme 4). As observed in our previous studies on the hydrogenation and C–H functionalization of the cyanthiwigin core,[20] oxygenation occurred selectively from the α-face of the molecule, likely due to steric shielding of the β-face by the methyl substituent at the B–C ring juncture. After unsuccessful attempts to open the epoxide under basic conditions (e.g., NaOH, $LiEt_3BH$), we found that treatment of epoxide **17** with catalytic perchloric acid delievered the desired *anti*-diol (**18**) in excellent yield.



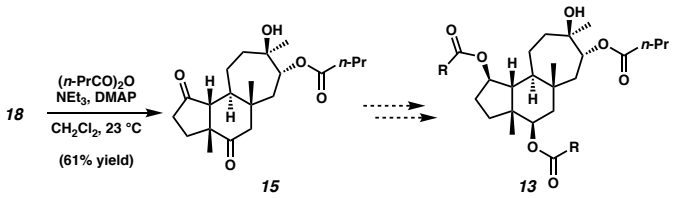
Scheme 4. Preparation of **18** via acid-catalyzed opening of **17**.

Pleased with this result, we proceeded to repeat the sequence on a larger scale. While epoxidation of **8** consistently occurred in excellent yield and facial selectivity, the acid-catalyzed epoxide-opening of **17** proved less reliable. When 50 mg of epoxide **17** was subjected to conditions that had been effective on 5 mg, the formation of multiple products was observed (Scheme 5). These compounds were isolated by column chromatography and characterized as compounds **18**–**23**. The desired *anti*-diol (**18**) comprised the major product at 32% yield while diastereomeric *anti*-diol **19** constituted the next most abundant product. Meinwald rearrangement[21] products **20** and **21** were formed in roughly equal amounts, and elimination products **22** and **23** were obtained in the smallest quantities.



Scheme 5. Formation of compounds **18**–**23** from **17** (50 mg).

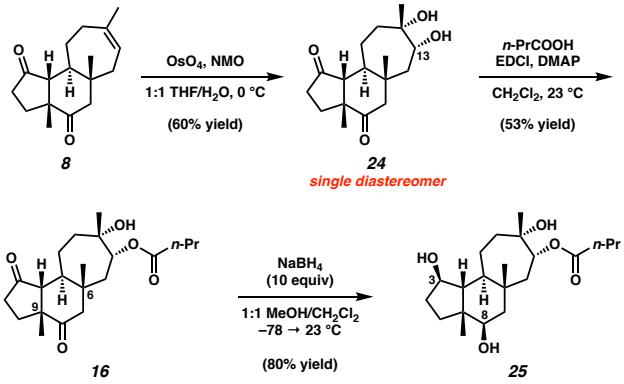
As evidenced by the low selectivity of this transformation, further exploration is needed to identify a scalable and reliable procedure for the preparation of *anti*-diol **18**.[22] In the meantime, we progressed diol **18** to tricyclic ester **15** en route to **13** (Scheme 6) and turned our attention toward synthesis of *syn*-diol-derived hybrids (**14**).



Scheme 6. Synthesis of **15** en route to cyanthiwigin–gagunin hybrids **13**.

2.2. Syn-diol route

Preparation of the *syn*-diol-derived hybrids commenced with dihydroxylation of **8** using osmium tetroxide and NMO (Scheme 7). We were pleased to find that *syn*-diol **24** was formed in good yield as a single diastereomer under these conditions. Diol **24** was subsequently treated with butyric acid, EDCI, and DMAP to achieve selective esterification of the secondary C13 hydroxyl, furnishing tricyclic mono-ester **16** in moderate yield. Treatment of **16** with excess sodium borohydride resulted in the formation of triol **25**, a key intermediate in the *syn*-diol route.



Scheme 7. Preparation of triol **25**.

Notably, hydride reduction occurred selectively from the α-face of diketone **16**, presumably due to steric factors as in previous cases. We propose that the C9 and C6 methyls control facial selectivity of reduction by blocking hydride approach from the Burgi–Dunitz angle[23] on the β-face. Thus, hydride attack occurs from the more accessible α-face despite the concavity of the three-dimensional architecture of **16**. This gives rise to the observed stereochemistry at C3 and C8 in the product (**25**) (Figure 3).

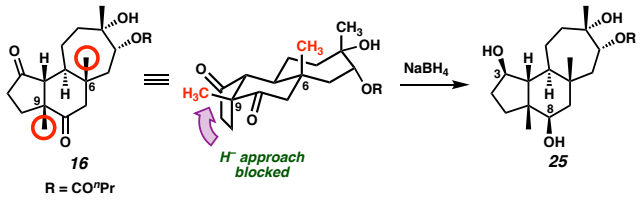
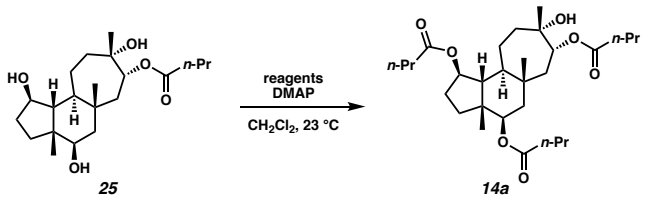


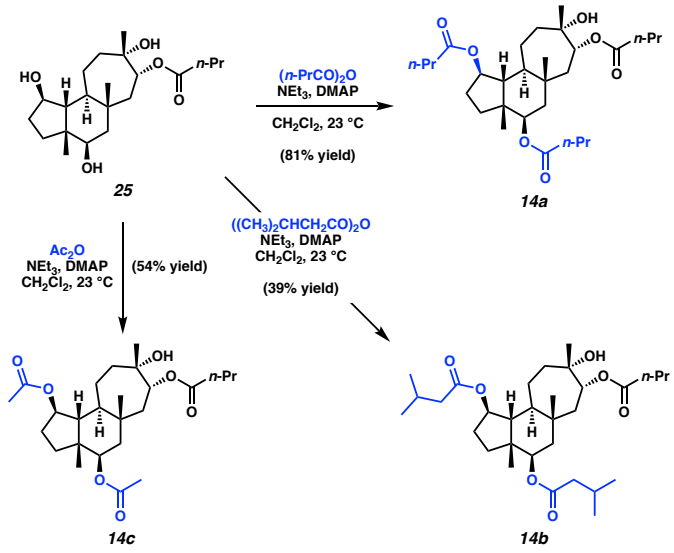
Figure 3. Stereochemical rationalization for formation of **25**.

With tris-hydroxylated intermediate **25** in hand, we proceeded to the final transformation in generating cyanthiwigin–gagunin hybrids **14**. Initial efforts at bis-esterification employing the same conditions used previously (butyric acid, EDCI, and DMAP) proved unsuccessful, returning large quantities of unreacted **25** (Table 1, Entry 1). Further attempts to access tri-ester **14a** using butyryl chloride and DMAP were also ineffective, instead producing a complex mixture of products (Entry 2). Finally, we discovered that the combination of butyric anhydride, triethylamine, and DMAP provided the optimal balance in reactivity, supplying cyanthiwigin–gagunin hybrid **14a** in high yield (Entry 3). Gratifyingly, application of these conditions to **25** using isovaleric anhydride or acetic anhydride enabled access to hybrids **14b** or **14c**, respectively (Scheme 8).



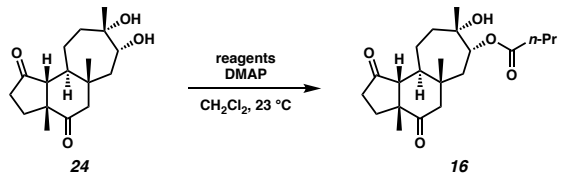
Entry	Reagents	Result
1	*n*-PrCOOH, EDCI	low conversion
2	*n*-PrCOCl	messy mixture
3	$(n\text{-PrCO})_2O$, NEt_3	81% yield of *14a*

Table 1. Optimization of esterification conditions for synthesis of cyanthiwigin–gagunin hybrid **14a**.



Scheme 8. Synthesis of cyanthiwigin–gagunin hybrids **14a**–**c** from common intermediate **25**.

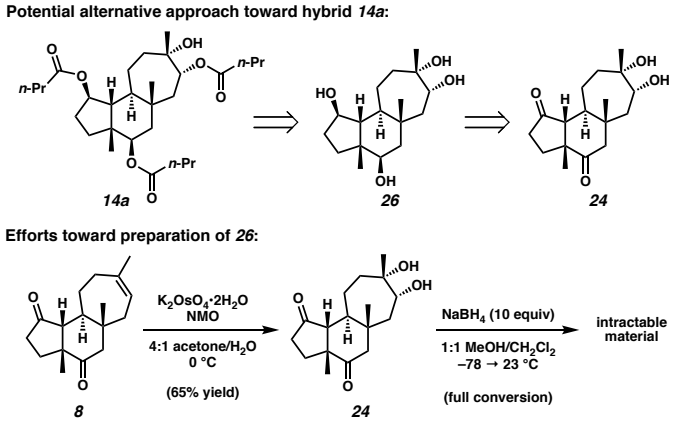
Noting the varying efficacies of esterification conditions employed in the preparation of **14a**, we re-examined the esterification of diol **24** (Table 2). Although the desired ester (**16**) was generated in serviceable quantities in every case, use of butyric anhydride and triethylamine in the presence of DMAP (Entry 3) resulted in significantly higher yields, in agreement with our previous findings.



Entry	Reagents	Yield
1	*n*-PrCOOH, EDCI	53%
2	*n*-PrCOCl	54%
3	$(n\text{-PrCO})_2O$, NEt_3	73%

Table 2. Comparison of conditions for esterification of **24**.

For the preparation of cyanthiwigin–gagunin hybrid **14a**, we wondered if a global esterification strategy might be feasible through tetra-hydroxylated intermediate **26** (Scheme 9). To investigate this possibility, we treated diol **24**, this time prepared through a catalytic dipotassium osmate dihydrate protocol, with excess sodium borohydride. Despite good conversion of **24**, the expected tetra-hydroxylated product (**26**) proved intractable, likely due to its high polarity and resistance to extraction from the aqueous layer. As such, we determined that a global esterification strategy through a tetra-hydroxylated intermediate was not a viable approach for the preparation of cyanthiwigin–gagunin hybrids containing three identical ester substituents.



Scheme 9. Investigation of a global esterification strategy toward hybrid **14a**.

2.3. Biological studies

Biological evaluation of synthetic intermediates has been carried out in collaboration with investigators at the City of Hope Comprehensive Cancer Center. Preliminary results indicate that compounds **14a**, **14b**, **14c**, **19**, **20**, **21**, **22**, **23**, and **25** do not exhibit significant potency against A2058 melanoma or DU145 prostate cancer cell lines at 10μM after 48 hours, but there remain opportunities for further evaluation of these and other compounds against more disease agents.

2.4. Future directions

True to the nature of late-stage diversification research programs, there exist an abundance of further avenues for cyanthiwigin–gagunin hybrid synthesis and biological

exploration. For each synthetic route to a hybrid molecule (e.g. *syn*-diol route, *anti*-diol route, etc.), there are nearly infinite combinations of ester functionalities that can be appended to the tricyclic core. Initial investigations have centered around butanoate, acetate, and isovalerate substituents based on their ubiquity among the natural gagunins, but as more insights into the activities of these compounds are gained, the ester functionalities can be re-designed to probe biological influence.

3. Conclusion

These investigations have revealed notable patterns of reactivity in the tricyclic framework of the cyanthiwigin and gagunin natural products. Transformations involving the C-ring olefin and the A- and B-ring carbonyls in **8** have enabled us to conclude that the β-face of the molecule is substantially less accessible than the α-face, likely due to steric hindrance originating from the C9 and C6 methyl substituents. We have prepared a variety of cyanthiwigin–gagunin hybrid molecules using a common late-stage intermediate (**25**) available in three steps from the cyanthiwigin natural product core (**8**). These compounds arose through a *syn*-dihydroxylation pathway, and after further optimization this strategy can also be employed in the preparation of hybrids through an *anti*-dihydroxylation pathway. Initial biological studies have not indicated appreciable cytotoxicity against melanoma and prostate cancer cell lines, but there remains much potential for further investigation.

In conclusion, a vast number of compounds are accessible through a multitude of synthetic pathways, including those yet to be examined. We anticipate that the synthetic insights derived from these exploratory studies will provide a strong foundation from which to launch further efforts toward the synthesis and biological evaluation of cyanthiwigin–gagunin hybrid molecules.

4. Experimental Section

4.1. General

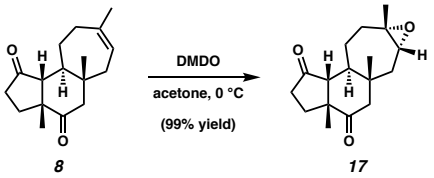
Unless noted in the specific procedure, reactions were performed in flame-dried glassware under argon atmosphere. Dried and deoxygenated solvents (Fisher Scientific) were prepared by passage through columns of activated aluminum before use.[24] Methanol (Fisher Scientific) was distilled from magnesium methoxide immediately prior to use. Commercial reagents (Sigma Aldrich or Alfa Aesar) were used as received. Triethylamine (Oakwood Chemical) was distilled from calcium hydride immediately prior to use. Dimethyldioxirane (DMDO) was prepared according to known procedure[25] immediately prior to use. Brine is defined as a saturated aqueous solution of sodium chloride. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-LCMS. TLC was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 spectrometer (500 MHz and 126 MHz, respectively), a Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (400 MHz and 101 MHz, respectively), a Varian Mercury 300 spectrometer (300 MHz and 75 MHz, respectively), or a Varian Inova 600 (at 600 MHz for ^{1}H NMR only) instrument, and are reported in terms of chemical shift relative to residual $CHCl_3$ (δ 7.26 and δ 77.16 ppm, respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations are used as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = complex multiplet. Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer using thin film samples on KBr plates and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer with fast atom bombardment (FAB+) ionization mode or were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+) mode. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm using a 100-mm path-length cell.

4.2. Preparative Procedures for anti-diol-derived hybrids

*4.2.1. Epoxide **17**.*

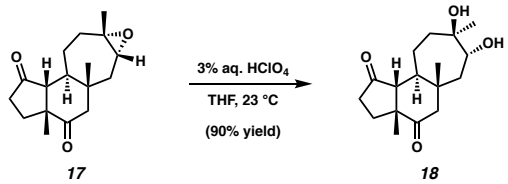
To a solution of tricyclic diketone **8** (50.0 mg, 0.192 mmol, 1.0 equiv) in acetone (2.0 mL) at 0 °C was added a solution of DMDO (0.0125M in acetone, 16.9 mL, 0.211 mmol, 1.1 equiv). The resulting mixture was stirred at 0 °C for 90 minutes, after which time the volatiles were removed under reduced pressure, affording epoxide **17** as a pale yellow oil (52.0 mg, 99% yield). This material was used without further purification. R_f = 0.36 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.72 (t, J = 7.5, 14.4 Hz, 1H), 2.65 (d, J = 14.7 Hz, 1H), 2.52 (dddd, J = 19.5, 10.3, 2.0, 0.9 Hz, 1H), 2.37 (dddd, J = 19.4, 10.2, 9.1, 1.2 Hz, 1H), 2.30–2.22 (m, 1H), 2.12 (td, J = 7.3, 2.8 Hz, 1H), 2.07 (d, J = 14.8 Hz, 1H), 2.05–1.94 (m, 2H), 1.90 (d, J = 12.2 Hz, 1H), 1.80–1.73 (m, 1H), 1.66 (ddd, J = 12.3, 11.1, 2.8 Hz, 1H), 1.55–1.48 (m, 1H), 1.45–1.37 (m, 1H), 1.33 (s, 3H), 1.30–1.24 (m, 1H), 1.11 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 217.7, 211.9, 62.5, 60.3, 59.3, 52.2, 50.7, 47.4, 43.8, 41.8, 34.4, 34.3, 31.3, 23.9, 22.2, 21.7, 17.0; IR (Neat Film, KBr) 2958, 2932, 1736, 1705, 1466, 1383, 1171, 1007, 875, 735 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1798, found 277.1789; $[\alpha]^{25}_D$ –68.4 (*c* 0.12, $CHCl_3$).



8 *17*

*4.2.2. Anti-diol **18**.*

To a solution of epoxide **17** (5.0 mg, 0.0181 mmol, 1.0 equiv) in THF (1.0 mL) at 23 °C was added perchloric acid (3 wt % solution in H_2O, 20 μL, 5.43 μmol, 0.3 equiv). The resulting mixture was stirred at 23 °C for 72 hours, after which time the reaction was diluted with ethyl acetate (5 mL) and washed with sat. aq. $NaHCO_3$ (5 mL), and brine (5 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated, and the crude residue was purified by silica gel column chromatography (30% → 40% → 50% → 60% → 75% ethyl acetate in hexanes) to afford *anti*-diol **18** as a colorless oil (4.8 mg, 90% yield). R_f = 0.10 (25% hexanes in ethyl acetate); ^{1}H



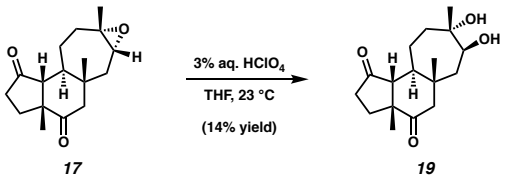
17 *18*

NMR ($CDCl_3$, 600 MHz) δ 3.88 (d, *J* = 10.1 Hz, 1H), 2.66 (d, *J* = 15.0 Hz, 1H), 2.53–2.44 (m, 1H), 2.41–2.33 (m, 1H), 2.27–2.21 (m, 1H), 2.16 (d, *J* = 15.0 Hz, 1H), 1.97–1.88 (m, 3H), 1.78–1.74 (m, 1H), 1.70–1.66 (m, 1H), 1.65 (m, 1H), 1.51 (m, 1H), 1.43 (m, 2H), 1.22 (s, 3H), 1.13 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 217.9, 212.2, 75.9, 74.1, 61.4, 52.9, 51.0, 46.5, 46.0, 41.8, 40.0, 34.3, 31.0, 24.5, 21.8, 19.9, 19.1; IR (Neat Film, KBr) 3444 (br), 2959, 2933, 1735, 1702, 1464, 1385, 1176, 1085, 992, 735 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{27}O_4$ $[M+H]^+$: 295.1909, found 295.1887; $[\alpha]^{25}_D$ –48.1 (*c* 1.62, $CHCl_3$).

4.2.3. Epoxide-opening side products ***19*****–*****23*****.***

To a solution of epoxide **17** (47.2 mg, 0.171 mmol, 1.0 equiv) in THF (8.5 mL) at 23 °C was added perchloric acid (3 wt % solution in H_2O, 0.17 mL, 0.0512 mmol, 0.3 equiv). The resulting mixture was stirred at 23 °C for 72 hours, after which time the reaction was diluted with ethyl acetate (10 mL) and washed with sat. aq. $NaHCO_3$ (10 mL), and brine (10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated, and the crude residue was purified by silica gel column chromatography (30% → 50% → 60% → 75% → 100% ethyl acetate in hexanes) to afford diol **18** (16.3 mg, 32% yield) along with side products **19**–**23**. Yields and chacaterization data for **19**–**23** are listed below.

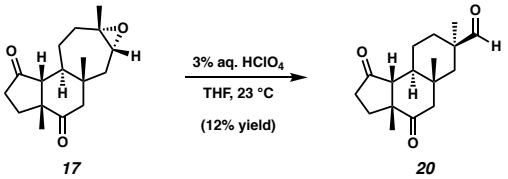
4.2.3.1. Diol ***19*****.**



17 ***19***

7.2 mg, 14% yield. R*f* = 0.15 (25% hexanes in ethyl acetate); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.85 (d, *J* = 10.3 Hz, 1H), 2.86 (d, *J* = 15.8 Hz, 1H), 2.60 (d, *J* = 6.7 Hz, 1H), 2.40–2.33 (m, 2H), 2.17 (d, *J* = 16.1 Hz, 1H), 2.08–2.04 (m, 1H), 1.96–1.91 (m, 2H), 1.86–1.83 (m, 1H), 1.73 (m, 1H), 1.60–1.54 (m, 1H), 1.51–1.46 (m, 2H), 1.29–1.27 (m, 1H), 1.20 (s, 3H), 1.19 (s, 3H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 221.7, 214.9, 75.8, 73.8, 60.1, 50.1, 49.0, 46.5, 44.9, 42.2, 39.8, 37.2, 32.4, 30.6, 24.8, 24.0, 21.5; IR (Neat Film, KBr) 3451 (br), 2958, 2932, 1737, 1704, 1455, 1384, 1268, 1169, 1147, 1087, 1070, 1036, 735 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{27}O_4$ $[M+H]^+$: 295.1909, found 295.1938; $[\alpha]^{25}_D$ –6.3 (*c* 0.72, $CHCl_3$).

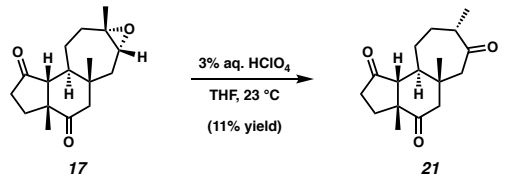
4.2.3.2. Aldehyde ***20*****.**



17 ***20***

5.5 mg, 12% yield. R*f* = 0.65 (25% hexanes in ethyl acetate); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.49 (d, *J* = 1.5 Hz, 1H), 2.52–2.46 (m, 2H), 2.42–2.36 (m, 1H), 2.35–2.30 (m, 1H), 2.29–2.23 (m, 2H), 2.19 (d, *J* = 14.8 Hz, 1H), 1.97 (dd, *J* = 14.2, 2.4 Hz, 1H), 1.88–1.83 (m, 2H), 1.81–1.75 (m, 1H), 1.54 (m, 1H), 1.23–1.17 (m, 1H), 1.12 (s, 3H), 1.11–1.07 (m, 1H), 0.94 (s, 3H), 0.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 217.2, 211.5, 205.0, 61.0, 52.4, 51.3, 48.4, 45.9, 41.3, 39.0, 34.3, 31.8, 31.3, 25.0, 21.8, 21.8, 18.4; IR (Neat Film, KBr) 2957, 2931, 1738, 1704 (overlapping peaks), 1456, 1384, 1135, 839 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1804, found 277.1819; $[\alpha]^{25}_D$ –41.5 (*c* 0.55, $CHCl_3$).

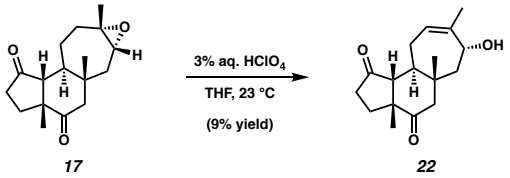
4.2.3.3. Triketone ***21*****.**



17 ***21***

5.2 mg, 11% yield. R*f* = 0.50 (25% hexanes in ethyl acetate); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.80 (d, *J* = 11.7 Hz, 1H), 2.74 (d, *J* = 15.0 Hz, 1H), 2.53 (dddd, *J* = 19.4, 10.3, 2.0, 0.8 Hz, 1H), 2.42 (m, 1H), 2.38–2.34 (m, 1H), 2.34–2.29 (m, 1H), 2.28–2.24 (m, 1H), 2.16–2.10 (m, 2H), 2.01–1.89 (m, 2H), 1.82–1.75 (m, 2H), 1.38–1.30 (m, 1H), 1.25–1.19 (m, 1H), 1.13 (s, 3H), 1.07 (d, *J* = 7.1 Hz, 3H), 0.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 217.6, 214.4, 211.4, 61.4, 54.2, 52.2, 50.9, 48.3, 46.5, 40.3, 34.3, 32.6, 31.2, 25.7, 21.7, 19.0, 18.6; IR (Neat Film, KBr) 2960, 2930, 1738, 1704 (overlapping peaks), 1456, 1384, 1222, 1176, 1053 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1804, found 277.1814; $[\alpha]^{25}_D$ –5.4 (*c* 0.52, $CHCl_3$).

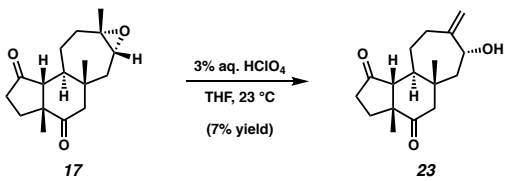
4.2.3.4. Allylic alcohol ***22*****.**



17 ***22***

4.3 mg, 9% yield. R*f* = 0.37 (25% hexanes in ethyl acetate); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.56–5.51 (m, 1H), 4.52 (d, *J* = 9.5 Hz, 1H), 2.93 (d, *J* = 14.9 Hz, 1H), 2.56–2.48 (m, 1H), 2.43–2.30 (m, 3H), 2.10 (d, *J* = 14.7 Hz, 1H), 1.97–1.90 (m, 2H), 1.87 (m, 1H), 1.77 (s, 3H), 1.75–1.69 (m, 2H), 1.58–1.54 (m, 1H), 1.11 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 218.2, 212.3, 143.1, 124.7, 69.6, 61.1, 52.9, 51.5, 49.1, 41.7, 41.6, 34.4, 31.1, 24.3, 21.7, 20.7, 19.6; IR (Neat Film, KBr) 3453 (br), 2960, 2923, 1737, 1704, 1462, 1384, 1164, 1124, 1051, 1002, 890, 735 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1804, found 277.1796; $[\alpha]^{25}_D$ –46.1 (*c* 0.43, $CHCl_3$).

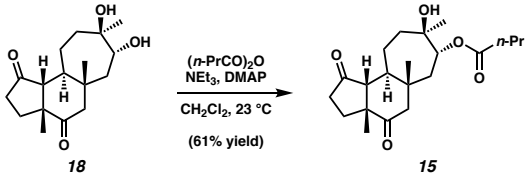
4.2.3.5. Allylic alcohol ***23*****.**



17 ***23***

3.4 mg, 7% yield. R*f* = 0.31 (25% hexanes in ethyl acetate); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.05 (s, 1H), 4.97 (s, 1H), 4.31 (dd, *J* = 10.1, 5.5 Hz, 1H), 2.71 (d, *J* = 14.6 Hz, 1H), 2.60–2.49 (m, 1H), 2.43–2.22 (m, 5H), 2.09 (d, *J* = 14.6 Hz, 1H), 1.89–1.81 (m, 1H), 1.80–1.71 (m, 4H), 1.22 (m, 1H), 1.10 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 217.8, 212.3, 153.6, 113.6, 71.1, 62.6, 53.0, 50.9, 49.1, 45.1, 41.1, 34.4, 31.3 (x2), 28.9, 21.7, 17.3; IR (Neat Film, KBr) 3437 (br), 2928, 2871, 1732, 1704, 1455, 1384, 1262, 1165, 1019, 995, 905 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1804, found 277.1803; $[\alpha]^{25}_D$ –47.6 (*c* 0.34, $CHCl_3$).

*4.2.4. Monoester **15**.*

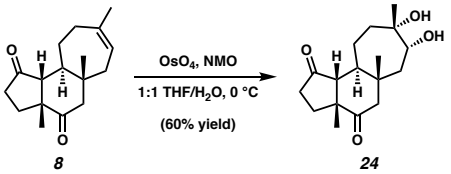


18 ***15***

To a solution of diol **18** (13.0 mg, 0.0442 mmol, 1.0 equiv) in dichloromethane (4.0 mL) was added triethylamine (25 μL, 0.177 mmol, 4.0 equiv), butyric anhydride (22 μL, 0.132 mmol, 3.0 equiv), and DMAP (2.7 mg, 0.0221 mmol, 0.5 equiv) at 23 °C. The resulting mixture was stirred for 30 minutes, after which time TLC analysis indicated full consumption of **18**. The reaction was diluted with dichloromethane (5 mL) and washed with water (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and the resulting crude residue was purified by silica gel column chromatography (10% → 30% → 50% ethyl acetate in hexanes) to afford monoester **15** as a colorless oil (9.8 mg, 61% yield). R*f* = 0.30 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.99 (d, *J* = 10.7 Hz, 1H), 2.55 (d, *J* = 15.0 Hz, 1H), 2.52–2.44 (m, 1H), 2.41–2.34 (m, 1H), 2.33 (t, *J* = 7.4 Hz, 2H), 2.21 (m, 1H), 2.13 (d, *J* = 15.1 Hz, 1H), 2.00–1.88 (m, 3H), 1.82–1.72 (m, 2H), 1.67 (q, *J* = 7.5 Hz, 2H), 1.61 (m, 1H), 1.50–1.37 (m, 3H), 1.14 (s, 3H), 1.14 (s, 3H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 217.7, 211.8, 174.4, 78.5, 75.1, 60.9, 52.7, 51.0, 47.2, 44.4, 41.6, 40.1, 36.6, 34.3, 31.1, 25.5, 21.8, 19.6, 18.6, 18.5, 13.8; IR (Neat Film, KBr) 3459 (br), 2963, 2933, 1732, 1705, 1463, 1456, 1380, 1260, 1177, 1086, 985 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{21}H_{31}O_4$ [M–OH]$^+$: 347.2217, found 347.2218; $[\alpha]^{25}_D$ –44.4 (*c* 0.26, $CHCl_3$).

4.3. Preparative Procedures for syn-diol-derived hybrids

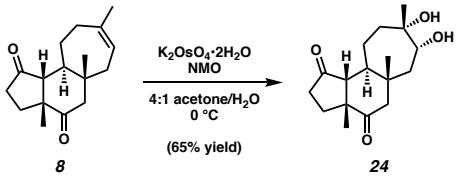
*4.3.1. Tricyclic Diol **24**.*



8 ***24***

To a solution of tricyclic diketone **8** (10 mg, 0.0384 mmol, 1.0 equiv) in 1:1 THF/H_2O (3.5 mL total volume) at 0 °C were added NMO (4 wt % solution in H_2O, 50 μL, 8.5 μmol, 0.22 equiv) and osmium tetroxide (50 wt % solution in H_2O, 0.1 mL, 0.410 mmol, 10.7 equiv). The resulting mixture was stirred at 0 °C for 4 hours, after which time TLC analysis showed full consumption of **8**. The reaction was quenched at 0 °C with saturated aq. $Na_2S_2O_3$ and stirred vigorously for 4 hours before being diluted with dichloromethane (15 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (30% → 50% → 70% → 90% ethyl acetate in hexanes) to afford tricyclic diol **24** as a colorless oil (6.7 mg, 60% yield). R_f = 0.10 (25% hexanes in ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.62 (d, *J* = 10.1 Hz, 1H), 2.73 (d, *J* = 15.2 Hz, 1H), 2.50 (dd, *J* = 19.6, 10.2 Hz, 1H), 2.35 (dd, *J* = 19.6, 9.5 Hz, 1H), 2.29–2.23 (m, 1H), 2.14 (d, *J* = 16.2 Hz, 1H), 2.05–1.98 (m, 2H), 1.95 (d, *J* = 14.5 Hz, 1H), 1.86 (m, 1H), 1.79 (d, *J* = 11.3 Hz, 1H), 1.76–1.72 (m, 1H), 1.52 (t, *J* = 25.0, 13.0 Hz, 1H), 1.32 (d, *J* = 14.6 Hz, 1H), 1.28 (s, 3H), 1.12 (s, 3H), 1.06–0.98 (m, 1H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 218.2, 212.4, 74.2, 72.9, 61.2, 53.1, 51.0, 46.6, 45.5, 40.9, 40.1, 34.3, 31.0, 27.9, 21.8, 20.2, 19.3; IR (Neat Film, KBr) 3448 (br), 2961, 2934, 1735, 1702, 1466, 1384, 1176, 1125, 916, 731 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{25}O_3$ [M–OH]$^+$: 277.1804, found 277.1804; $[\alpha]^{25}_D$ –225.2 (*c* 1.00, $CHCl_3$).

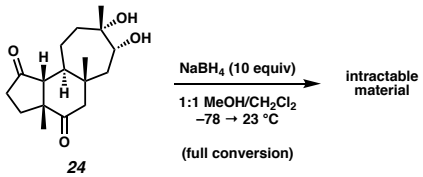
*4.3.2. Dihydroxylation of **8** using dipotassium osmate dihydrate.*



8 ***24***

To a solution of tricyclic diketone **8** (50 mg, 0.192 mmol, 1.0 equiv) in 4:1 acetone/H_2O (10 mL total volume) at 0 °C were added NMO (45.0 mg, 0.384 mmol, 2.0 equiv) and dipotassium osmate dihydrate (7.1 mg, 0.0192 mmol, 0.1 equiv). The resulting mixture was stirred at 0 °C for 7 hours, after which time TLC analysis showed full consumption of **8**. The reaction was quenched with saturated aq. $Na_2S_2O_3$ at 0 °C and stirred vigorously for 30 minutes before being diluted with dichloromethane (15 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (50% → 75% → 100% ethyl acetate in hexanes) to afford tricyclic diol **24** as a colorless oil (36.8 mg, 65% yield).

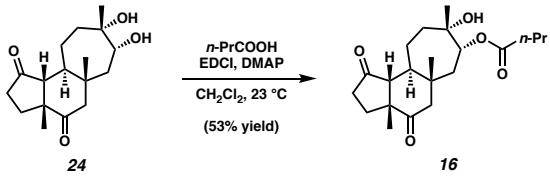
*4.3.3. Sodium borohydride reduction of diol **24**.*



24

To a solution of diol **24** (5.7 mg, 0.0194 mmol, 1.0 equiv) in 1:1 CH_2Cl_2/MeOH (2.0 mL total volume) was added a solution of sodium borohydride (7.3 mg, 0.194 mmol, 10.0 equiv) in 1:1 CH_2Cl_2/MeOH (0.5 mL total volume) at –78 °C. The reaction mixture was allowed to warm to 23 °C over the course of six hours. When TLC analysis indicated full consumption of starting material, the reaction was quenched with acetone (1.0 mL) and 2N NaOH (1.0 mL). The phases were separated, and the organic layer was immediately washed with brine (10 mL) and dried over sodium sulfate. After filtration and concentration under reduced pressure, the crude residue was subjected to silica gel column chromatography (100% ethyl acetate), but tetra-hydroxylated compound **26** was not obtained.

*4.3.4. Tricyclic monoester **16**.*

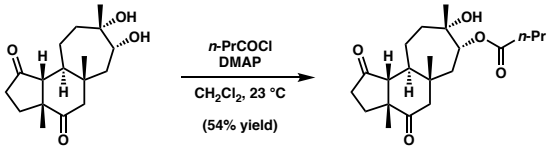


24 ***16***

To a solution of diol **24** (6.7 mg, 0.0228 mmol, 1.0 equiv) in dichloromethane (1.0 mL) at 23 °C were added EDCI (6.5 mg, 0.0342 mmol, 1.5 equiv), DMAP (2.8 mg, 0.0228 mmol, 1.0 equiv), and butyric acid (3.2 μL, 0.0342 mmol, 1.5 equiv). The resulting mixture was stirred at 23 °C for 24 hours, after which time the reaction was diluted with ethyl acetate (5 mL) and

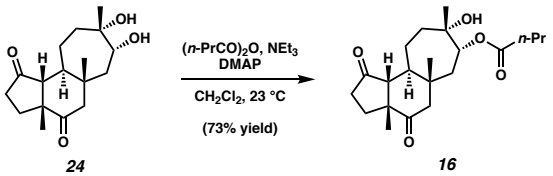
washed with 0.5 M HCl (3 mL), sat. aq. $NaHCO_3$ (3 mL), and brine (3 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated, and the crude residue was purified by silica gel column chromatography (15% → 25% → 35% → 55% ethyl acetate in hexanes) to afford monoester **16** as a colorless oil (4.4 mg, 53% yield). R_f = 0.33 (25% hexanes in ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.86 (d, *J* = 10.6 Hz, 1H), 2.55 (d, *J* = 15.1 Hz, 1H), 2.53–2.46 (m, 1H), 2.41–2.34 (m, 1H), 2.32 (t, *J* = 7.4 Hz, 2H), 2.27–2.17 (m, 2H), 2.14 (d, *J* = 15.2 Hz, 1H), 2.07–2.01 (m, 1H), 2.01–1.95 (m, 1H), 1.88 (d, *J* = 12.6 Hz, 1H), 1.79–1.73 (m, 1H), 1.70–1.64 (m, 3H), 1.55 (m, 1H), 1.20 (s, 3H), 1.17 (d, *J* = 14.3 Hz, 1H), 1.14 (s, 3H), 1.13–1.07 (m, 1H), 0.94 (t, *J* = 7.4, 14.8 Hz, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 218.0, 211.8, 172.7, 74.6, 73.5, 61.1, 52.6, 50.9, 47.4, 43.3, 40.2, 40.0, 36.5, 34.3, 31.1, 28.6, 21.8, 20.2, 18.6, 18.0, 13.8 ; IR (Neat Film, KBr) 3503 (br), 2964, 2934, 2875, 1735, 1705, 1458, 1379, 1258, 1177, 988, 732 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{31}O_4$ $[M–OH]^+$: 347.2222, found 347.2229; $[\alpha]^{25}_D$ –277.4 (*c* 1.00, $CHCl_3$).

*4.3.5. Esterification of **24** using butyryl chloride.*



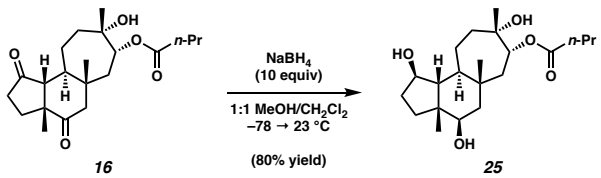
To a solution of diol **24** (30.0 mg, 0.102 mmol, 1.0 equiv) in 3:1 CH_2Cl_2/pyridine (4.0 mL total volume) at 23 °C were added butyryl chloride (53 μL, 0.510 mmol, 5.0 equiv) and DMAP (12.5 mg, 0.102 mmol, 1.0 equiv). The resulting mixture was stirred at 23 °C for 2 hours, after which time the reaction was cooled to 0 °C and quenched with H_2O (5.0 mL) and saturated aq. NH_4Cl (5.0 mL), then extracted with ethyl acetate (2 x 10 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (15% → 30% → 45% ethyl acetate in hexanes) to afford monoester **16** as a colorless oil (20.2 mg, 54% yield).

*4.3.6. Esterification of **24** using butyric anhydride.*



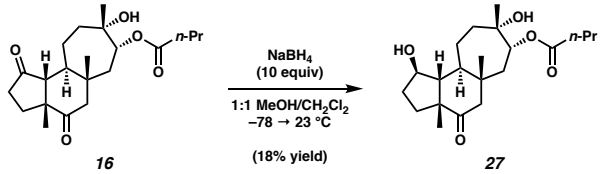
To a solution of diol **24** (36.8 mg, 0.125 mmol, 1.0 equiv) in dichloromethane (6.5 mL) was added triethylamine (70 μL, 0.500 mmol, 4.0 equiv), butyric anhydride (60 μL, 0.375 mmol, 3.0 equiv), and DMAP (7.6 mg, 0.0625 mmol, 0.5 equiv) at 23 °C. The resulting mixture was stirred for 1 hour, after which time TLC analysis indicated full consumption of **24**. The reaction was diluted with dichloromethane (10 mL) and washed with water (2 x 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and the resulting crude residue was purified by silica gel column chromatography (25% → 40% → 60% ethyl acetate in hexanes) to afford monoester **16** as a colorless oil (33.3 mg, 73% yield).

*4.3.7. Tris-hydroxylated tricycle **25**.*



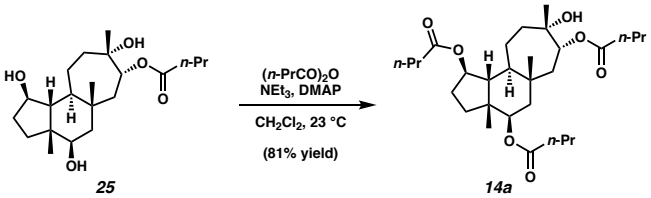
To a solution of diketone **16** (31.0 mg, 0.0851 mmol, 1.0 equiv) in dichloromethane (2.0 mL) and methanol (2.0 mL) was added a solution of sodium borohydride (32.2 mg, 0.851 mmol, 10.0 equiv) in dichloromethane (1.0 mL) and methanol (1.0 mL) at –78 °C. The reaction mixture was allowed to warm to 23 °C over the course of 6 hours. When TLC analysis indicated full consumption of starting material, the reaction was quenched with acetone (2.0 mL) and 2N NaOH (2.0 mL). The phases were separated, and the organic layer was immediately washed with brine (10 mL) and dried over sodium sulfate. After filtration and concentration under reduced pressure, the crude residue was purified by silica gel column chromatography (15% ethyl acetate in hexanes), furnishing triol **25** (25.0 mg, 80% yield). **Triol 25:** R_f = 0.19 (25% hexanes in ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.87 (dd, *J* = 11.1, 2.5 Hz, 1H), 4.01 (td, *J* = 6.2, 2.9 Hz, 1H), 3.69 (dd, *J* = 8.7, 5.8 Hz, 1H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.06–1.99 (m, 1H), 1.99–1.95 (m, 1H), 1.94–1.88 (m, 1H), 1.84–1.78 (m, 1H), 1.73–1.62 (m, 6H), 1.60 (m, 1H), 1.53–1.50 (m, 2H), 1.38–1.35 (m, 1H), 1.34–1.32 (m, 1H), 1.26–1.23 (m, 1H), 1.18 (s, 3H), 1.13 (s, 3H), 1.12 (s, 3H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.8, 80.5, 76.4, 74.2, 73.3, 57.6, 46.4, 45.9, 45.7, 45.1, 39.3, 37.5, 36.6, 35.0, 33.4, 29.6, 23.2, 22.5, 21.5, 18.7, 13.9; IR (Neat Film, KBr) 3402 (br), 2933, 2874, 1715, 1463, 1384, 1307, 1263, 1196, 1097, 1032, 916, 732 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{21}H_{36}O_5K$ $[M+K]^+$: 407.2194, found 407.2196; $[\alpha]^{25}_D$ –20.7 (*c* 1.00, $CHCl_3$).

*4.3.8. Mono-reduction product **27**.*



A mono-reduction product, diol **27**, was also generated from the borohydride reduction of **16** described above and was isolated separately from the column (5.6 mg, 18% yield). **Diol 27:** R_f = 0.25 (25% hexanes in ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.90 (d, *J* = 10.7 Hz, 1H), 4.19 (t, *J* = 5.3, 2.1 Hz, 1H), 2.35–2.26 (m, 4H), 2.14–2.06 (m, 3H), 1.81–1.76 (m, 2H), 1.75–1.71 (m, 1H), 1.70–1.65 (m, 3H), 1.63–1.59 (m, 2H), 1.31 (s, 3H), 1.27–1.24 (m, 2H), 1.22 (s, 3H), 1.18–1.13 (m, 1H), 0.96 (t, *J* = 7.1, 14.8 Hz, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 214.7, 172.7, 80.5, 74.8, 73.7, 60.5, 53.7, 53.1, 52.5, 43.3, 40.7, 38.3, 36.9, 36.6, 34.5, 28.8, 23.9, 22.6, 18.6, 18.2, 13.8; IR (Neat Film, KBr) 3443 (br), 2964, 2934, 1731, 1694, 1463, 1384, 1264, 1190, 1140, 1030, 992, 920, 732 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{35}O_5$ $[M+H]^+$: 367.2484, found 367.2471; $[\alpha]^{25}_D$ –21.9 (*c* 1.21, $CHCl_3$).

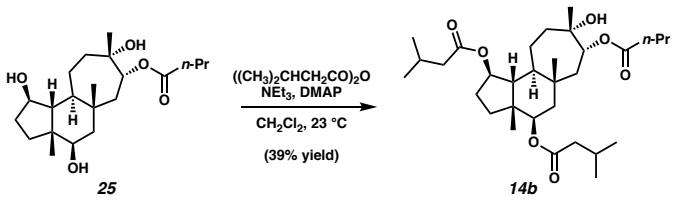
*4.3.9. Cyanthiwigin–gagunin hybrid **14a**.*



To a solution of tricyclic triol **25** (10.2 mg, 0.0277 mmol, 1.0 equiv) in dichloromethane (2.0 mL) was added triethylamine (30 μL, 0.222 mmol, 8.0 equiv), butyric anhydride (30 μL, 0.166 mmol, 6.0 equiv), and DMAP (3.4 mg, 0.0277 mmol, 1.0 equiv) at 23 °C. The resulting mixture was stirred for 2 hours, after which time TLC analysis indicated full consumption of **25**. The reaction was diluted with dichloromethane (5 mL) and washed

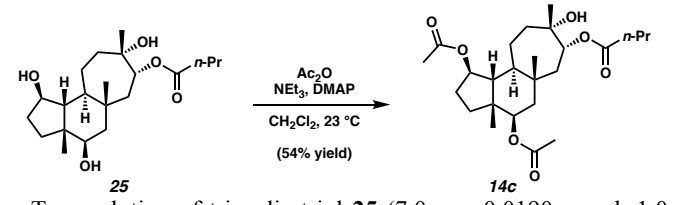
with water (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and the resulting crude residue was purified by silica gel column chromatography (10% → 40% → 60% ethyl acetate in hexanes) to afford cyanthiwigin–gagunin hybrid **14a** as a colorless oil (11.4 mg, 81% yield). R*f* = 0.16 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.10–5.06 (m, 1H), 4.95–4.89 (m, 2H), 2.32–2.29 (m, 2H), 2.28–2.23 (m, 4H), 2.01 (ddd, *J* = 14.9, 7.4, 3.1 Hz, 1H), 1.94 (dd, *J* = 13.9, 10.9 Hz, 1H), 1.88–1.82 (m, 1H), 1.74–1.69 (m, 2H), 1.69–1.61 (m, 8H), 1.59 (d, *J* = 4.3 Hz, 1H), 1.56–1.51 (m, 3H), 1.24 (m, 2H), 1.19 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H), 1.06–1.01 (m, 1H), 0.99–0.92 (m, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.2, 173.2, 172.8, 81.4, 75.7, 74.0, 73.9, 53.5, 46.8, 45.1, 44.4, 41.9, 40.6, 36.9, 36.8, 36.6, 36.1, 34.6, 29.5, 29.5, 23.7, 22.8, 19.2, 18.6, 18.6, 18.5, 13.9, 13.8 (x2); IR (Neat Film, KBr) 3506 (br), 2966, 2936, 2876, 1731, 1461, 1384, 1258, 1184, 1144, 1092, 981 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{29}H_{49}O_7$ $[M+H]^+$: 509.3478, found 509.3464; $[\alpha]^{25}_D$ –11.4 (*c* 1.14, $CHCl_3$).

*4.3.10. Cyanthiwigin–gagunin hybrid **14b**.*



To a solution of tricyclic triol **25** (5.4 mg, 0.0147 mmol, 1.0 equiv) in dichloromethane (1.0 mL) was added triethylamine (16 μL, 0.118 mmol, 8.0 equiv), isovaleric anhydride (17 μL, 0.0879 mmol, 6.0 equiv), and DMAP (1.8 mg, 0.0147 mmol, 1.0 equiv) at 23 °C. The resulting mixture was stirred for 1 hour, after which time TLC analysis indicated full consumption of **25**. The reaction was diluted with dichloromethane (5 mL) and washed with water (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and the resulting crude residue was purified by silica gel column chromatography (10% → 30% ethyl acetate in hexanes) to afford cyanthiwigin–gagunin **14b** as a colorless oil (3.1 mg, 39% yield): R*f* = 0.70 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.11–5.08 (m, 1H), 4.98–4.91 (m, 2H), 2.32 (t, *J* = 7.4, 14.8 Hz, 2H), 2.27–2.21 (m, 1H), 2.21 (s, 1H), 2.20–2.16 (m, 4H), 2.16–2.08 (dddd, *J* = 12.9, 9.5, 8.1, 6.3 Hz, 2H), 2.05–1.99 (m, 1H), 1.96 (dd, *J* = 14.0, 11.0 Hz, 1H), 1.85 (m, 1H), 1.83 (s, 1H), 1.74–1.71 (m, 1H), 1.71–1.67 (m, 2H), 1.66–1.60 (m, 2H), 1.57–1.52 (m, 2H), 1.31–1.28 (m, 1H), 1.28–1.23 (m, 2H), 1.21 (s, 3H), 1.12 (s, 3H), 1.10 (s, 3H), 1.00–0.95 (m, 15H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.8, 172.7, 172.7, 81.3, 75.7, 74.0, 73.9, 53.5, 46.6, 45.1, 44.4, 44.2, 44.0, 42.0, 40.5, 36.6, 36.2, 34.7, 29.6, 29.5, 25.9, 25.7, 23.8, 22.9, 22.7, 22.7, 22.6, 22.6, 19.3, 18.7, 13.9; IR (Neat Film, KBr) 3499 (br), 2961, 2874, 1731, 1466, 1384, 1294, 1257, 1189, 1120, 1095, 990 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{31}H_{51}O_6$ $[M–OH]^+$: 519.3686, found 519.3700; $[\alpha]^{25}_D$ –13.7 (*c* 0.31, $CHCl_3$).

*4.3.11. Cyanthiwigin–gagunin hybrid **14c**.*



To a solution of tricyclic triol **25** (7.0 mg, 0.0190 mmol, 1.0 equiv) in dichloromethane (2.0 mL) was added triethylamine (21 μL, 0.152 mmol, 8.0 equiv), acetic anhydride (11 μL, 0.114 mmol, 6.0 equiv), and DMAP (2.3 mg, 0.0190 mmol, 1.0 equiv) at 23 °C. The resulting mixture was stirred for 1 hour, after which time TLC analysis indicated full consumption of **25**. The reaction was diluted with dichloromethane (5 mL) and washed with water (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and the resulting crude residue was purified by silica gel column chromatography (20% → 40% ethyl acetate in hexanes) to afford cyanthiwigin–gagunin **14c** as a colorless oil (4.5 mg, 54% yield): R*f* = 0.56 (40% hexanes in ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.08–5.05 (m, 1H), 4.93 (dd, *J* = 10.9, 1.8 Hz, 1H), 4.89 (t, *J* = 4.1 Hz, 1H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.26–2.17 (m, 1H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02–1.98 (m, 1H), 1.94 (dd, *J* = 13.9, 10.9 Hz, 1H), 1.81 (s, 1H), 1.75–1.70 (m, 2H), 1.69–1.65 (m, 2H), 1.64–1.60 (m, 1H), 1.59–1.52 (m, 4H), 1.26–1.22 (m, 2H), 1.20 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H), 1.05 (ddd, *J* = 11.9, 9.7, 1.7 Hz, 1H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.8, 170.7, 170.6, 81.6, 75.7, 74.3, 74.0, 53.4, 46.8, 45.0, 44.4, 41.8, 40.6, 36.6, 36.1, 34.7, 29.5, 29.5, 23.6, 22.9, 21.6, 21.5, 19.2, 18.7, 13.9; IR (Neat Film, KBr) 3457 (br), 2966, 2934, 2877, 1732, 1463, 1384, 1245, 1184, 1145, 1022, 982, 908 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{41}O_7$ $[M+H]^+$: 453.2852, found 453.2835; $[\alpha]^{25}_D$ –12.3 (*c* 0.42, $CHCl_3$).

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Supplementary Material

PDFs of NMR (^{1}H, ^{13}C, 2-D) and IR data for all new compounds are available online at DOI:

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