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The total synthesis of (±)-arisugacin A

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This paper is dedicated to Professor Gilbert Stork on the occasion of his 80th birthday

Abstract—A 20-step total synthesis of (±)-arisugacin A with an overall yield of 2.1% is described here in detail. This synthesis features a formal [3+3] cycloaddition reaction of α,β-unsaturated iminium salts with 6-aryl-4-hydroxy-2-pyrones through a highly stereoselective 6π-electron electrocyclic ring-closure of 1-oxatriene. A strategic dihydroxylation–deoxygenation protocol leading to the desired angular C12a–OH was developed to serve as a critical step in leading to the final total syntheses of arisugacin A. This synthetic endeavor also led to an interesting and unexpected retro-aldol–aldol sequence in the AB-ring.

1. Introduction

Arisugacin A (**1**), isolated from *Penicillium* Sp. Fo-4259 by Ōmura, is a potent and selective inhibitor of acetylcholinesterase with an IC_{50} of 1 nM,[1] thereby possessing significance in treatment of dementia diseases such as Alzheimer's disease.[2] Given its biological relevance and unique meroterpenoidal structure (a hybrid of polyketide and terpenoid) that resembles other important natural products such as the territrems (**3**)[3] and pyripyropenes,[4] we have investigated a number of different synthetic routes seeking an efficient synthesis of arisugacin A.[5–8] In particular, we have been developing a formal [3+3] cyclo-addition method[9–11] that involves condensing α,β-unsaturated iminium salts **7** with 6-aryl-4-hydroxy-2-pyrones such as **8** through a stereoselective 6π-electron electrocyclic ring-closure[12] of the 1-oxatriene intermediate **10** (Fig. 1).

In this tandem Knoevenagel condensation–pericyclic ring-closure sequence,[13] two σ-bonds and a new stereocenter adjacent to the oxygen atom are formed, leading to a convergent synthesis of the advanced pentacyclic intermediate **6**[7,8] in a highly stereoselective manner (C6a in **6**). We have applied this stepwise cycloaddition to total syntheses of pyranoquinoline alkaloids[14] and expanded it to synthesis of dihydropyridines using vinylogous amides.[15] Recently, Ōmura's group and ours independently communicated total syntheses of (±)-arisugacin A featuring this

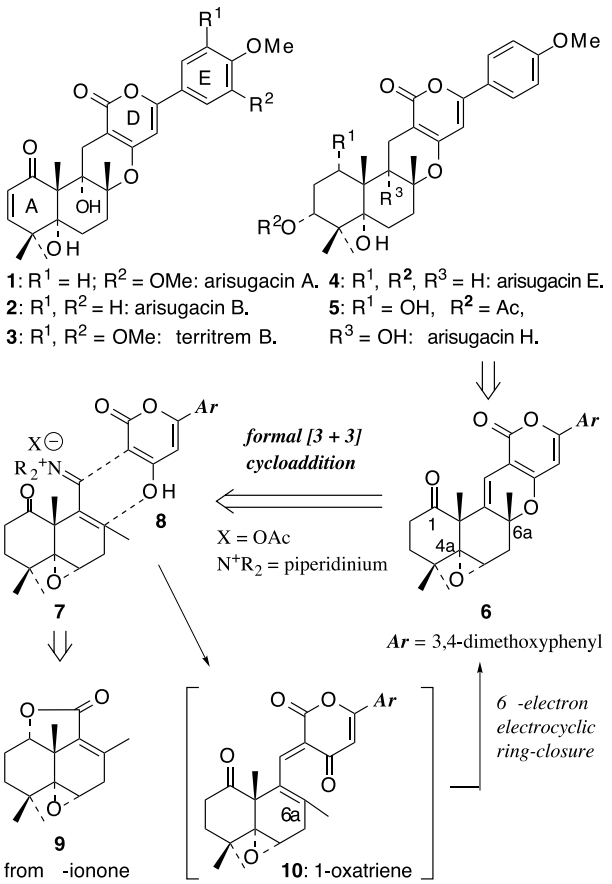

Figure 1.

Keywords: arisugacin A; formal [3+3] cycloaddition; iminium salts; stereoselective pericyclic ring-closure; retro-aldol–aldol sequence.

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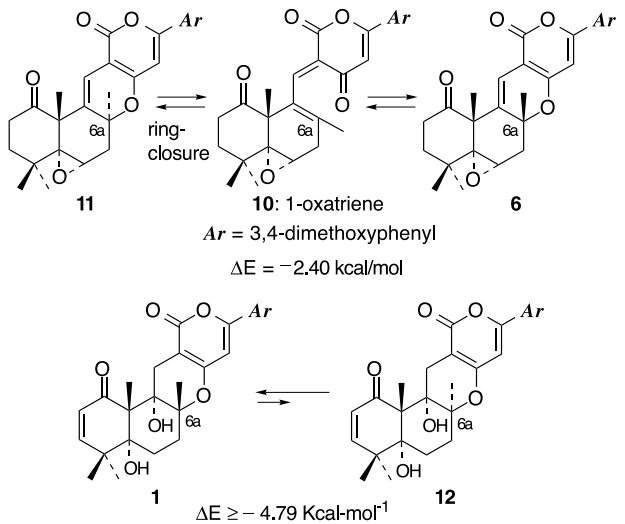
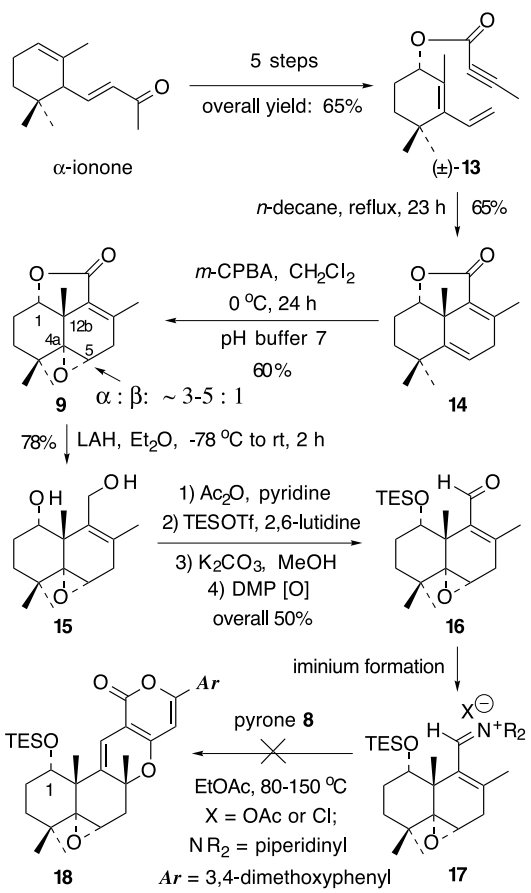


Figure 2.

stepwise cycloaddition reaction.[16–18] We report here the full details of our success in applying the formal [3+3] cycloaddition to a total synthesis of (±)-arisugacin A.

2. Results and discussion

Although the proposed route in Figure 1 is quite feasible based on our understanding of the key formal [3+3] cycloaddition step (**7**+**8**→**6**),[9] there are two major uncertainties that could render this effort completely futile. First, sterically congested α,β-unsaturated iminium salts such as **7** can impede the formal [3+3] cycloaddition.[9] Secondly, and more significantly, in our hands,[14b] there had been no successful stereoselective examples of this particular formal cycloaddition using chiral α,β-unsaturated iminium salts except in one isolated case.[10b] Thus, the ability to control the stereochemistry at C6a through this key formal [3+3] cycloaddition reaction remained speculative.



Scheme 1.

However, because the 6π-electron electrocyclic ring-closure of the respective 1-oxatriene **10** has been found to be reversible,[9,15a] a favorable diastereoselectivity could still be achieved leading to the thermodynamically more stable isomer **6** in which the C6a methyl is β in the event that **11** is the initial major product. The pentacycle **6** is more favored than its C6a-epimer **11** (the C6a methyl is α) by about 2.40 kcal mol^{-1} using PM3 calculations (Spartan™). In addition, calculations showed that the natural product arisugacin A (**1**) itself is more stable with a β-C6a-methyl than **12** (C6a methyl is α) by ca. 4.79 kcal mol^{-1} (Fig. 2).

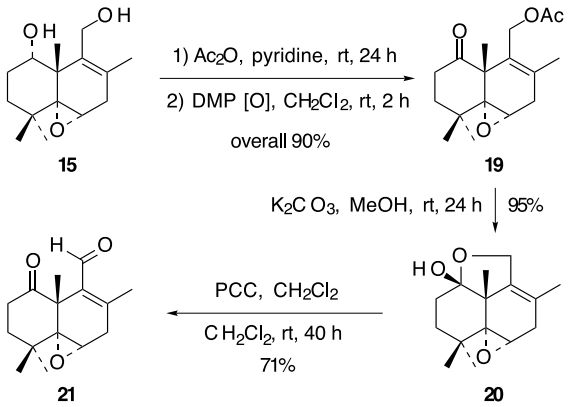
2.1. The epoxy diol route

Encouraged by this calculation, the racemic ester **13** was prepared readily in 5 steps from α-ionone in 65% overall yield via a known sequence used in the synthesis of forskolin (Scheme 1).[19] The subsequent intramolecular Diels–Alder reaction of **13** in refluxing anhydrous *n*-decane gave the tricyclic lactone **14** in 65% yield.[20] Epoxidation of **14** using buffered *m*-CPBA led to the α-epoxy lactone **9** in 60% yield. The corresponding β-epoxy isomer was also isolated in 10–20% yield but can be readily separated from the α-epoxy isomer **9**. The relative stereochemistry of **9** was assigned using nOe experiments.

It is noteworthy that stereochemical control of the two new stereogenic centers at C4a and C12b ultimately stems from the stereochemistry at C1 through the intramolecular Diels–Alder reaction. Hence, an optically pure **13** should lead to an enantioselective preparation of the α-epoxy lactone **9**, thereby ultimately leading to an enantioselective synthesis of arisugacin A (**1**). LAH reduction of the α-epoxy lactone **9** led to the epoxy diol **15** in 78% yield with the epoxide remained intact when carried out at low temperature. Standard functional group manipulations provided the aldehyde **16** in 4 steps with an overall yield of 50%.

However, under our conditions[9] as well as a variety of other conditions,[21,22] the formal [3+3] cycloaddition reaction of the iminium salt **17** with the pyrone **8** failed to provide any desired pentacycle **18**. This failure prompted us to think that **17** could be sterically too demanding, thereby obstructing the reaction pathway.[8]

Molecular models revealed that if either the C1 carbon were sp^2 hybridized or the C1 hydroxyl group were unprotected, such a steric congestion could be alleviated. We chose the former option as shown in Scheme 2. Acetylation of the diol **15** followed by Dess–Martin periodinane (DMP) oxidation afforded the ketone **19** in 90% overall yield. Deacetylation of **19** led to the formation of the lactol **20**, and PCC

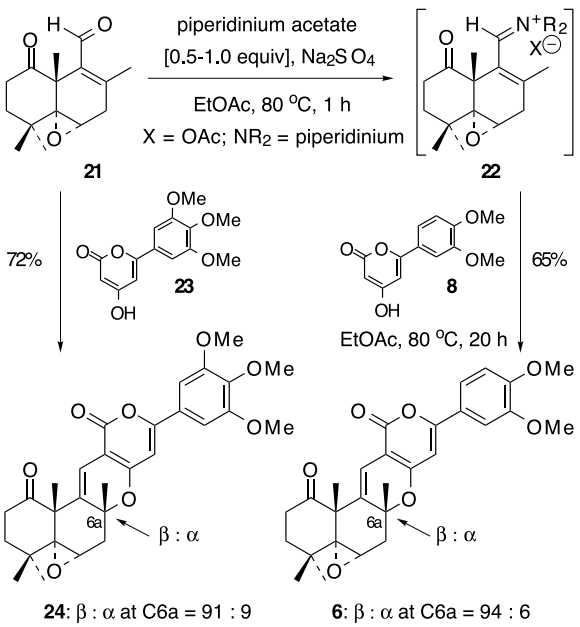


Scheme 2.

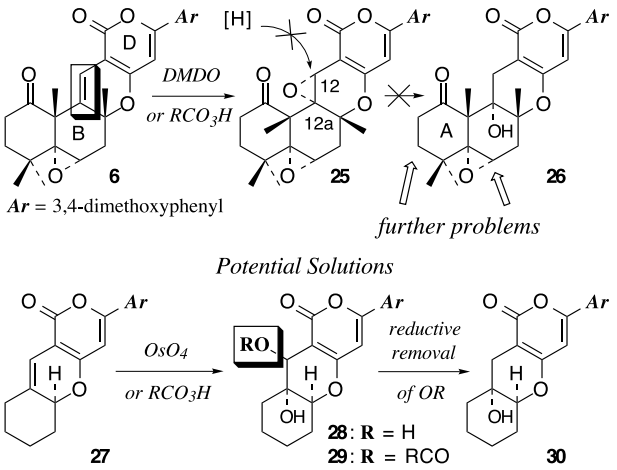
oxidation successfully unraveled the lactol **20** and gave the desired keto aldehyde **21** in 71% yield. Attempts to go from **15** to **21** directly via a double Swern oxidation were not fruitful.

The keto aldehyde **21** proved to be quite suitable for constructing the pentacycle **6**. The iminium intermediate **22** was generated from **21** using 0.5–1.0 equiv. piperidinium acetate in the presence of Na_2SO_4 at 80°C for 1 h (Scheme 3). The subsequent reaction of **22** with the pyrone **8** in EtOAc at 80°C for 20 h led to the isolation of the pentacycle **6** in 65% yield with a diastereomeric ratio of 94:6. The angular methyl at C6a was established as β for the major isomer of **6** and α for the minor isomer (**11**) by using nOe experiments.

By using the pyrone **23**[23] under the same conditions, the pentacycle **24** was obtained in 72% yield with a diastereomeric ratio of 91:9 also in favor of the same major isomer. The compound **24** contains the desired E-ring leading to territrem B (**3**). The high diastereoselectivity obtained in these reactions here is likely a result of the reversible 6π-electron electrocyclic ring-closure.[9,15a] The



Scheme 3.



Scheme 4.

minor isomer **11** (C6a methyl being α) from the reaction that led to **6** could be cleanly separated and equilibrated completely to the major isomer **6** (with C6a methyl being β) when subjected again to the reaction conditions, thereby supporting our assertion made earlier.

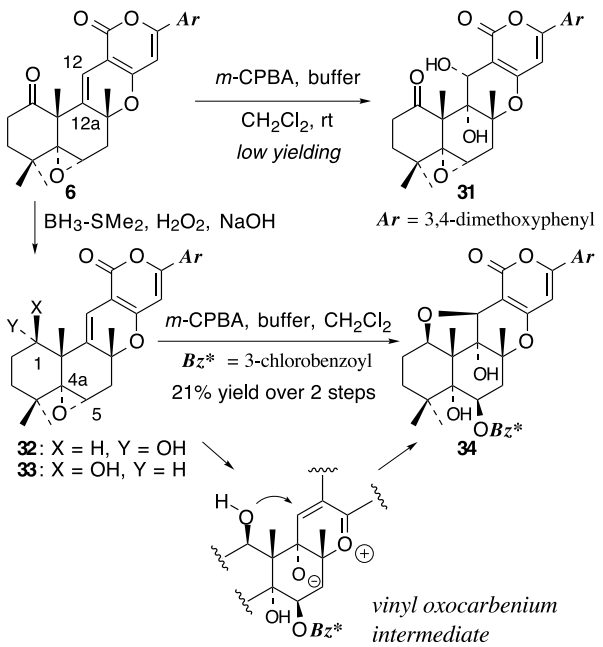
2.2. Problems with the epoxy diol route

The above 13-step preparation of the pentacycle **6** in 9% overall yield from α-ionone firmly establishes the feasibility of the formal [3+3] cycloaddition reaction as an approach to arisugacin A (**1**) and its family members as well as structural analogs. However, a major challenge lay ahead that led to a 14-month investigation involving installation of the C12a hydroxyl group in the C-ring. The sequence of epoxidation–reduction was met with difficulties because ring opening of the C12a–C12 epoxide in **25** by various nucleophilic oxygen species precluded the addition of hydride (Scheme 4). The desired product **26** was never isolated.

To solve this problem, bisoxygenation or dihydroxylation of the model tetracycle **27** was carried out followed by removal of the more activated secondary oxygen functionality in **28** or **29** using reductive methods that we had developed for these specific systems (Scheme 4).[24,25] The effort in developing this methodology (**27** to **30**) turned out to be significant not only in this synthetic endeavor but also for future total syntheses employing the formal [3+3] cycloaddition reaction.

Based on our model study (**27** to **30**),[24,25] the C12–C12a olefin in the C-ring of epoxy pentacycle **6** was subjected to a variety of epoxidation and dihydroxylation conditions but all failed (see supplementary materials for more details on various conditions). The only discernable product arising from these attempts was the diol **31** in only 8–21% yield when using *m*-CPBA, but this result was also difficult to reproduce (Scheme 5). Attempts to hydroborate the same C12–C12a olefin in **6** using BH_3–SMe_2 gave exclusively the alcohol **33** with β-C1–OH based on nOe experiments. The alcohol **33** was also obtained when **6** was reduced using Dibal-H or $NaBH_4$.

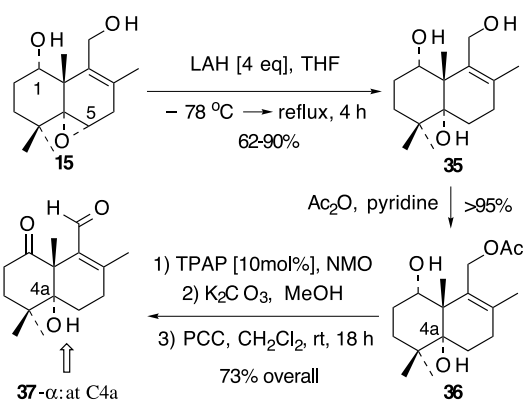
Epoxidation of **33** using *m*-CPBA buffered with $NaHCO_3$ led to the hexacycle **34** in 21% overall yield starting from **6**.



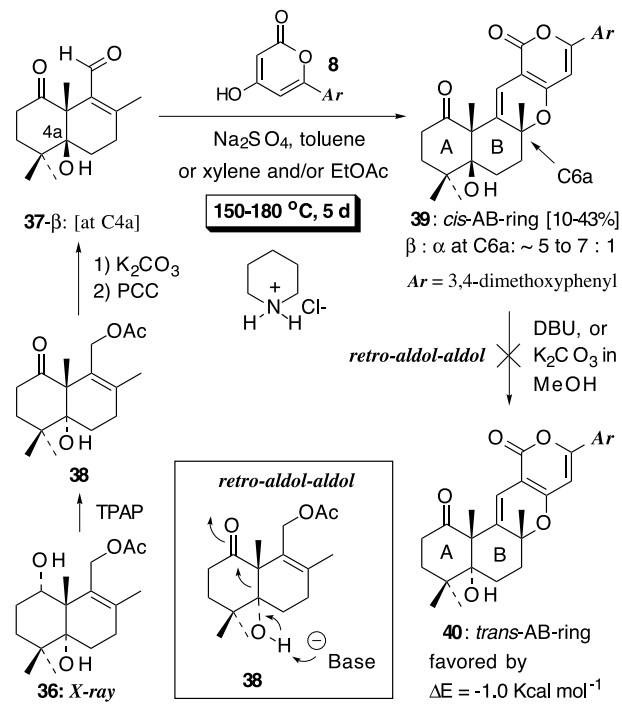
Scheme 5.

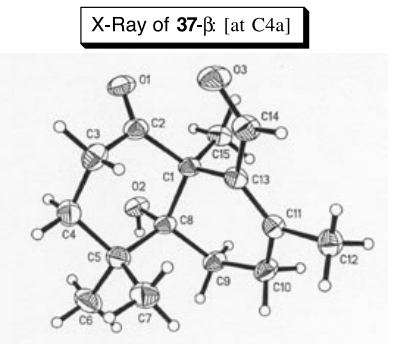
Stereochemistry of the hexacycle **34** was assigned using nOe experiments. This indicates that not only epoxidation of the C12–C12a olefin had taken place, but also the ring opening of the C12–C12a epoxide had occurred. This presumably took place through a vinyl oxocarbenium intermediate that was trapped intramolecularly by the β-C1–OH leading to the new furan ring, although such an event could also take place without involving the proposed zwitterion. Furthermore, C4a–C5 epoxide in the B-ring had surprisingly ring-opened at the same time.

Reductive removal of the 3-chlorobenzoyl group (*Bz* ∗) in **34** using Dibal-H (63% yield) led to a free alcohol at C5 that was subjected to xanthate formation (CS_2, MeI, 52% yield).[21] However, the subsequent Barton's deoxygenation proceeded only in very low yield in removing the C5 oxygen functionality of **34**. Ultimately, there were other additional problems associated with ring opening of the C4a–C5 epoxide (see supplementary materials), thereby completely suffocating this route. The most significant result turned out to be the hindsight recognition that the C1–OH group has to



Scheme 6.





Scheme 7.

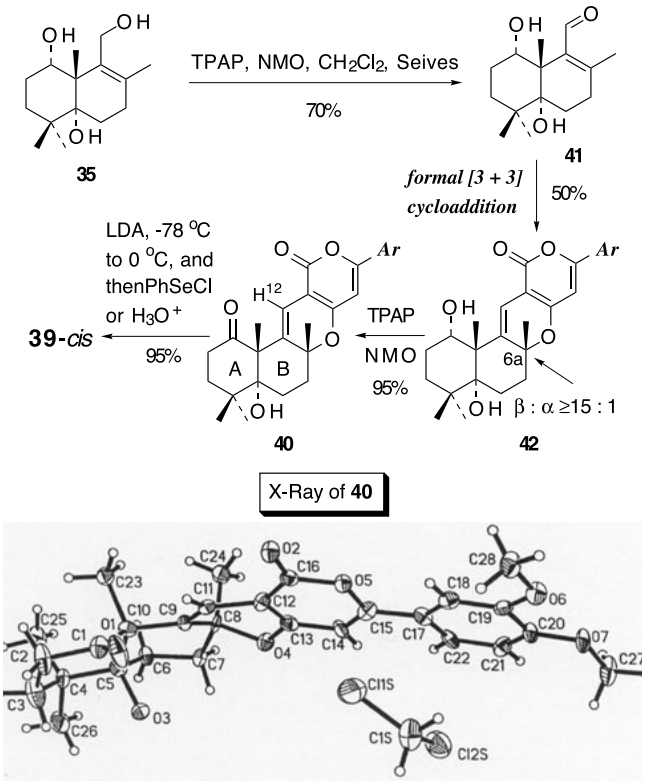
be beta to allow successful functionalization of the C12–C12a olefin in the C-ring.

2.3. The triol route

To avoid the C4a–C5 epoxide issue, a new route to the keto enal "**37**-α" was pursued (Scheme 6). The triol **35** could be attained via LAH reduction of **15**, and acylation of **35** would lead to the acetate **36** whose stereochemistry was corroborated by X-ray analysis. The subsequent TPAP oxidation of **36** followed by deacylation and PCC oxidation led to the keto-enal "**37**-α" in 73% overall yield.

It was not readily apparent that the assignment of keto enal "**37**-α" was incorrect until we pursued the subsequent formal [3+3] cycloaddition of the alleged "**37**-α" with the pyrone **8**. The reactions of keto enal "**37**-α" with **8** could only proceed at high temperatures using the more reactive piperidinium hydrochloride salt[21] leading to the pentacycle **39** with low yield and poor diastereoselectivity (Scheme 7).

An X-ray structural analysis disturbingly showed while the connectivity was correct, it was not the keto enal "**37**-α" but **37**-β that had led to the wrong pentacycle **39** (see



Scheme 8.

supplementary materials) and not the desired pentacycle **40** with *trans*-fused AB-ring.[26] It is reasonable to propose that a retro-aldol–aldol sequence had occurred during preparation of **37** at the stage of deacylation of **38** using K_2CO_3/MeOH (see the box in Scheme 7). Calculations (AM1-Spartan™) showed that *cis*-fused decalin motif in **37**-α is actually more stable than **37**-α by ~1.5 kcal mol^{-1} presumably due to the severe interactions between the two axial methyl groups in the *trans*-decalin motif of **37**-α.

On the other hand, the desired pentacycle **40** was calculated (AM1-Spartan™) to be more stable than **39** by ~1.0 kcal mol^{-1}, but attempts using K_2CO_3/MeOH or DBU to equilibrate **39** to **40** via another retro-aldol–aldol sequence all failed (see supplementary materials).[26]

To avoid this unexpected retro-aldol–aldol predicament, desired pentacycle **40** was prepared via yet another route. As shown in Scheme 8, the triol **35** was oxidized using Ley's TPAP oxidation without protecting either the C1- or C4a-hydroxyl group to give the diol enal **41** in 70% yield. This chemoselectivity likely was a result of a shorter reaction time in favor of the more reactive primary allyl alcohol. The diol enal **41** was surprisingly stable and did not lactolize unless it was subjected to elevated temperatures or acidic conditions.[26]

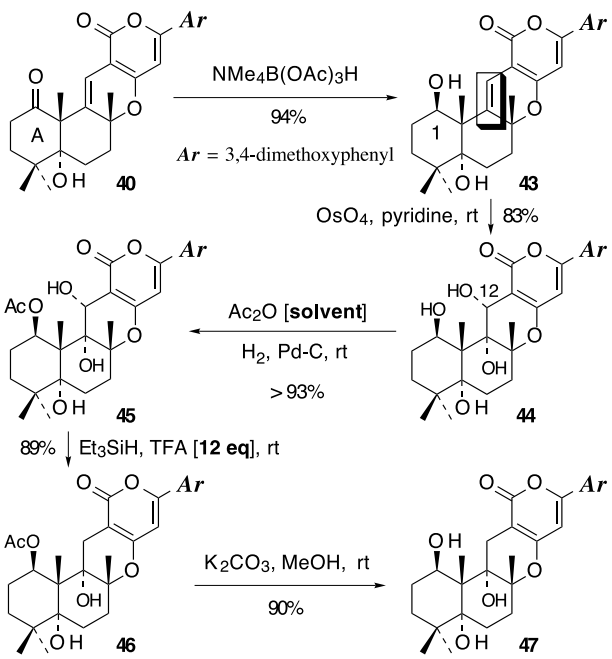
Reaction of the diol enal **41** with **8** under the standard [3+3] conditions led to the desired pentacyle **42** essentially as a single diastereomer with an improved 50% yield. Subsequent oxidation of **42** using Ley's TPAP afforded the pentacycle **40** in 95% yield. The relative stereochemistry was unambiguously confirmed using X-ray analysis. The X-ray structure of **40** also explains the unusually downfield shifted olefinic ^1H in the C-ring (7.43 ppm), whereas the same olefinic ^1H in **39**-*cis* is at the expected region (6.09 ppm). The ^1H in **40** experiences diamagnetic anisotropic effect due to its close proximity to the A-ring carbonyl oxygen.[26]

When the pentacyle **40** was treated with 2.0 equiv. of LDA followed by addition of PhSeCl, **40** was found to have isomerized completely to the pentacycle **39** likely via a similar retro-aldol–aldol sequence. The propensity of **40** to epimerize to **39** back to implies that **39** could actually be the thermodynamically more stable structure.

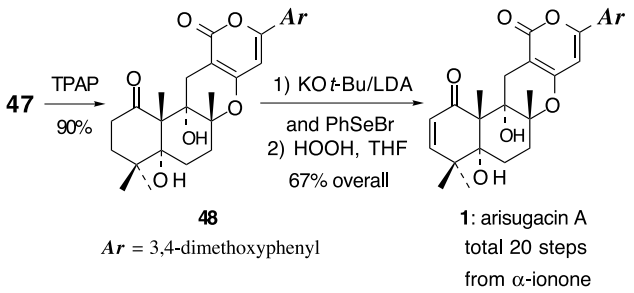
2.4. The final total synthesis

Advanced pentacycles **42** and **40** provided new opportunities in achieving a total synthesis of (±)-arisugacin A (**1**). However, attempts at oxidizing the C-ring olefin in **42** using various protocols all failed (see supplementary materials). These failures suggest that the stereochemistry of the C1–OH group likely plays a significant role sterically. Given our earlier success in epoxidizing the epoxy pentacycle **32** having the β-C1–OH (see Scheme 5), the pentacycle **40** was subjected to directed reduction using $NMe_4B(OAc)_3H$ in AcOH to give exclusively the diol **43** in 94% yield with β-C1–OH (Scheme 9, also see supplementary materials).[26]

Dihydroxylation[24,25] of **43** using a stoichiometric amount of OsO_4 in pyridine gave the desired tetraol **44** in 83% yield as a single diastereomer. The removal of the C12–OH in **44** using the Et_3SiH protocol[24,25] gave an undesired hexacycle structurally similar to **34**.[27] Hydrogenation of **44** using Ac_2O as solvent[24,25] gave instead the triol acetate **45** in 93% yield, suggesting that acylation of the C1–OH had taken place. The triol acetate **45** could also be obtained quantitatively using Ac_2O and DMAP, providing exclusive acylation at the β-C1–OH.



Scheme 9.



Scheme 10.

Subsequent removal of the C12–OH in **45** using Et_3SiH and 12 equiv. of TFA gave **46** in 89% yield.[24,25] The reductive cleavage was selective for the more reactive allylic C-12 hydroxyl group. Such chemoselectivity is also possible due to the assistance from the pyranyl oxygen atom for the C-12 hydroxyl group is essentially situated in the gamma position of an enol-ether. Deacylation of **46** gave the desired triol **47** in 90% yield.

Ley's TPAP oxidation of the triol **47** led to the pentacycle **48** in 90% yield (Scheme 10). To circumvent the retro-aldol–aldol that was observed earlier for **40**, protocols such as DDQ and IBX[29] were examined to install the double bond in the A-ring but were not successful. Schlosser's base, prepared from deprotonating diisopropyl amine with *n*-BuLi in the presence of KO*t*-Bu, proved to be effective in the selenation using PhSeBr. This outcome is presumably due to some counter cation effect since LDA or KHMDS did not work well. Subsequent oxidative elimination of the selenide intermediate using H_2O_2 led to (±)-arisugacin A (**1**) in 67% yield for the two steps. The synthetic sample matched spectroscopically [co-spectra of ^1H NMR in pyridine-d_5] and analytically [TLC: in 2:1 EtOAc/hexane: 2:1 ether/hexane; 1:9 acetone/$CHCl_3$] with (+)-arisugacin A.

3. Conclusions

We have described here a 20-step total synthesis of (±)-arisugacin A with an overall yield of 2.1%. This synthesis features a formal [3+3] cycloaddition reaction of α,β-unsaturated iminium salts with 6-aryl-4-hydroxy-2-pyrones through a highly stereoselective 6π-electron electrocyclic ring-closure of 1-oxatriene. A strategic dihydroxylation–deoxygenation protocol leading to the desired angular C12a–OH was developed to serve as a critical step in the final total synthesis of arisugacin A. Our synthetic endeavor also led to an interesting observation of an unexpected retro-aldol–aldol sequence in the AB-ring.

4. Experimental

4.1. General

All reactions performed in flame-dried glassware under nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased (Aldrich, Acros), except where noted. Chromatographic separation were performed using Bodman 60 Å SiO_2. ^1H and ^{13}C NMR spectra were obtained on Varian VI-300, VX-300, and VI-500 spectrometers using $CDCl_3$ (except where noted) with TMS or residual solvent as standard. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were obtained using NaCl plates on a Midac M2000 FTIR. TLC analysis was performed using Aldrich 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV and vanillin or $KMnO_4$ stains. Low resolution mass spectra were obtained using an Agilent 1100 series LS/MSD and are APCI. High resolution mass spectral analyses performed at University of Minnesota Department of Chemistry Mass Spectrometry Laboratory. X-Ray analyses performed at University of Minnesota Department of Chemistry X-ray facility. All spectral data obtained for new compounds are reported here.

4.1.1. Ketone 6. A heterogeneous mixture of enal **21** (8.2 mg, 33 μmol), pyrone **8** (10.0 mg, 40 μmol), Na_2SO_4 (3.0 mg) and piperidinium acetate (3.0 mg, 21 μmol) in dry ethyl acetate (1.5 mL) was sealed in a 3 mL vial and heated to 90°C. After 18 h, the mixture was filtered through a pad of silica, concentrated, and purified by flash chromatography (60% EtOAc in hexanes) to afford the title compound (10.3 mg, 65%) as a bright yellow solid in a diastereomeric ratio of 94:6 with the desired isomer being major.

6: ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (s, 3H), 1.17 (s, 3H), 1.43 (s, 3H), 1.53 (s, 3H), 1.66–1.72 (m, 1H), 1.97–2.03 (m, 1H), 2.38–2.45 (m, 2H), 2.80–2.86 (m, 2H), 3.32 (d, 1H, J=4.5 Hz), 3.93 (s, 3H), 3.94 (s, 3H), 6.10 (s, 1H), 6.38 (s, 1H), 6.90 (d, 1H, J=8.5 Hz), 7.29 (s, 1H), J=2.0 Hz), 7.38 (dd, 1H, J=2.0, 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 25.1, 26.7, 28.6, 33.8, 35.2, 36.3, 36.9, 52.4, 52.9, 56.0, 56.1, 66.6, 77.9, 96.2, 101.5, 108.3, 111.0, 112.9, 119.1, 124.6, 132.4, 149.2, 151.5, 160.2, 161.5, 163.7, 211.8; IR (film) cm^{-1} 1271, 1515, 1550, 1714, 2944, 2968; mass spectrum (EI): *m/e* (%relative intensity) 478 $(M)^+$ (50), 463 $(M-CH_3)^+$ (100), 435 (32), 165 (99), 149 (69), 69 (86); *m/e* calcd for $C_{28}H_{30}O_7$ 478.1992; found 478.1999.

4.1.2. Ester 13. The allylic alcohol (100.0 mg, 590 μmol), 2-butynoic acid (75.0 mg, 1.5 equiv.) and DCC (200.0 mg, 1.6 equiv.) were dissolved in CH_2Cl_2 (10.0 mL) and cooled to 0°C. DMAP (20.0 mg) in CH_2Cl_2 (3.0 mL) was added dropwise, and the reaction placed in the refrigerator overnight. The resulting mixture was filtered through a coarse frit to remove precipitated *N*,*N*′-dicyclohexyl urea. The liquid portion was washed with 1 M HCl (5 mL), brine (5 mL), and dried (Na_2SO_4). Removal of solvent in vacuo, followed by silica gel chromatography (7% EtOAc in hexanes) afforded the ester (132.0 mg, 96%) as a clear oil.

13: R_f=0.63 (10% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 3H), 1.03 (s, 3H), 1.40 (ddd, 1H, J=3.3, 6.6, 13.2 Hz), 1.64 (m, 1H), 1.69 (s, 3H), 1.78 (dddd, 1H, J=3.3, 4.2, 6.6, 14.1 Hz), 1.92 (dddd, 1H, J=3.3, 4.8, 10.8, 14.4 Hz), 1.98 (s, 3H), 5.02 (dd, 1H, J=2.7, 18.0 Hz), 5.28 (dd, 1H, J=4.5, 4.5 Hz), 5.31 (dd, 1H, J=2.4, 11.4 Hz), 6.17 (dqdd, 1H, J=1.2, 1.2, 11.4, 17.4 Hz).

4.1.3. Lactone 14. Ester **13** (12.4 g, 52.9 mmol) was dissolved in *n*-decane (750 mL) in a 1 L flask. A condenser was attached and the system purged with nitrogen. The solution was heated to reflux (180°C) for 28 h. After

cooling, solvent was removed under high vacuum (0.1 mmHg, 40°C) and the residue was purified by flash silica gel chromatography (10% EtOAc in hexanes) to afford the lactone (7.29 g, 59%) as a clear oil along with recovered ester (1.43 g, 12%).

14: R_f=0.48 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.16 (ddd, 1H, J=4.5, 7.0, 18.0 Hz), 1.20 (s, 3H), 1.21 (s, 3H), 1.43 (ddd, 1H, J=3.5, 13.5, 13.5 Hz), 1.59 (ddd, 1H, J=4.5, 14.0, 14.0 Hz), 1.90 (dddd, 1H, J=3.5, 3.5, 3.5, 13.0 Hz), 2.25 (s, 3H), 2.78 (dd, 1H, J=6.0, 21.0 Hz), 2.91 (d, 1H, J=21.0 Hz), 4.30 (dd, 1H, J=5.0, 12.5 Hz), 5.66 (dd, 1H, J=2.0, 6.5 Hz).

4.1.4. Lactone 9. Lactone **14** (175.0 mg, 0.753 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Solid *m*-CPBA (77%, 254.0 mg, 1.13 mmol) was then added in one portion and the solution placed in the refrigerator for 2 d. Precipitated *m*-chlorobenzoic acid was removed by filtration through a coarse fritted funnel, and the filtrate diluted with chilled CH_2Cl_2 (25 mL). The filtrate was then washed successively with cold 1 M NaOH (5 mL), H_2O (5 mL), and brine (5 mL). Drying (Na_2SO_4), concentration in vacuo, and flash chromatography (20% EtOAc in hexanes) afforded the β-epoxide (10–20% dependant on trial) and the desired α-epoxide (109.0 mg, 59%) as a colorless oil.

9: R_f=0.20 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81, (s, 3H), 1.21 (s, 3H), 1.32 (s, 3H), 1.37 (ddd, 1H, J=1.5, 14.0, 14.0 Hz), 1.55 (dddd, 1H, J=2.5, 12.0, 12.0, 14.0 Hz), 1.67 (ddd, 1H, J=2.5, 5.0, 14.0 Hz), 1.98 (dddd, 1H, J=2.5, 5.0, 5.5, 12.5 Hz), 2.16 (s, 3H), 2.60 (dd, 1H, J=3.0, 18.0 Hz), 2.73 (d, 1H, J=18.5 Hz), 3.10 (d, 1H, J=3.5 Hz), 4.16 (dd, 1H, J=5.5, 11.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 25.3, 25.7, 26.8, 29.8, 33.4, 34.7, 44.8, 48.3, 66.3, 84.1, 126.8, 146.0, 168.7; mass spectrum (EI): *m/e* (%relative intensity) 248 $(M)^+$ (65), 149 (31), 121 (39), 105 (40), 91 (41), 84 (100); *m/e* calcd for $C_{15}H_{20}O_3$ 248.1412; found 248.1409.

4.1.5. Diol 15. To a solution of lactone **9** (113.0 mg, 455 μmol) in ether (10 mL) at −78°C was added a solution of LAH (1 M in THF, 1.80 mL, 1.80 mmol). After 2 h at −78°C, the solution was allowed to warm to rt and quenched with saturated ammonium chloride (10 mL). The organic layer was separated, and the aqueous phase extracted with EtOAc (3×10 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (10 mL), brine (10 mL), and dried (Na_2SO_4). Concentration, followed by flash chromatography (gradient, 25–50% EtOAc in hexanes) afforded the title diol (71.2 mg, 62%) as a white solid.

15: mp=147.5–148.0°C; R_f=0.13 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 3H), 1.14 (s, 3H), 1.20 (s, 3H), 1.27 (m, 1H), 1.78 (s, 3H), 1.80–1.94 (m, 2H), 2.05 (ddd, 1H, J=2.4, 4.2, 15.0 Hz), 2.44 (d, 1H, J=18.6 Hz), 2.53 (dd, 1H, J=2.7, 18.6 Hz), 3.23 (dd, 1H, J=2.4, 2.4 Hz), 3.69 (brs, 1H), 4.01 (d, 1H, J=12.3 Hz), 4.12 (dd, 1H, J=3.9, 3.9 Hz), 4.23 (d, 1H, J=12.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 23.2, 25.5, 26.5, 26.8, 31.2, 32.1, 35.0, 45.2, 52.0, 57.7, 66.7, 73.5, 128.6, 134.4; IR (film) cm^{-1} 1437, 2907, 2846, 2990, 3370; mass spectrum (EI): *m/e* (%relative intensity) 216 $(M-2H_2O)^+$ (31), 177 (100), 161 (41), 149 (98), 135 (49), 123 (86), 107 (79), 91 (61), 81 (63), 55 (53).

4.1.6. Aldehyde 16. Acetic anhydride (1.0 mL) was added dropwise to a solution of diol **15** (54.0 mg, 214 μmol) in pyridine (4 mL) at rt. After 24 h, the solution was diluted with CH_2Cl_2 (30 mL), washed with saturated $NaHCO_3$ (30 mL), dried (Na_2SO_4), and concentrated under vacuum (ca. 1 mmHg) to remove solvents. Flash chromatography (1:6 EtOAc/hexanes) afforded the monoacetylated intermediate (60.2 mg, 96%) as a white solid.

Monoacetylated intermediate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (s, 3H), 1.18 (s, 3H), 1.19 (s, 3H), 1.15–1.24 (m, 1H), 1.75–1.80 (m, 1H), 2.01 (s, 3H), 1.92–2.07 (m, 2H), 2.48 (s, 2H), 2.55 (d, 1H, J=6.3 Hz), 3.14 (t, 1H, J=1.8 Hz), 4.00 (s, 1H), 4.78 (d, 1H, J=2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 21.1, 23.5, 25.4, 26.8, 26.9, 31.3, 32.4, 34.7, 45.2, 51.0, 60.7, 66.2, 72.0, 130.1, 132.4, 170.9; IR (film) cm^{-1} 1243 m, 1725 vs, 2916 m, 2988 s, 3524 brs; mass spectrum (EI): *m/e* (%relative intensity) 294 $(M)^+$ (5), 279 $(M-CH_3)^+$ (29), 261 (27), 234 $(M-AcOH)^+$ (5), 219 (17), 216 $(M-H_2O-AcOH)^+$ (14), 201 (19), 173 (23), 159 (54), 149 (48), 135 (100), 119 (52), 107 (33), 91 (35), 81 (46), 69 (22), 55 (32).

To a solution of the mono-acetylated intermediate (described above) (17.8 mg, 60.5 μmol) in CH_2Cl_2 (2.0 mL) at rt was added 2,6-lutidine (8 drops) and TESOTf (6 drops) sequentially. After 4 h, the solution was filtered through a pad of silica, concentrated, and the crude residue purified by flash chromatography (1:13 EtOAc/hexanes) to afford the TES ether/acetate (20.1 mg, 81%) as a colorless oil.

TES ether/acetate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.63 (q, 6H, J=7.7 Hz), 0.79 (s, 3H), 0.96 (t, 9H, J=7.8 Hz), 1.11–1.15 (m, 1H), 1.16, (s, 3H), 1.17 (s, 3H), 1.67 (s, 3H), 1.65–1.72 (m, 1H), 2.01 (s, 3H), 1.90–2.11 (m, 2H), 2.46 (s, 2H), 2.96 (t, 1H, J=2.1 Hz), 4.13 (t, 1H, J=1.8 Hz), 4.70 (d, 1H, J=12.6 Hz), 4.79 (d, 1H, J=12.6 Hz).

To a solution of the TES ether (described above) (20.1 mg, 49.2 μmol) in methanol (2.5 mL) at rt was added a solution of K_2CO_3 (35.0 mg, 253 μmol) in H_2O (0.5 mL). After 2 d, the reaction mixture was diluted with ether (20 mL), washed with brine (20 mL), dried (Na_2SO_4), concentrated, and the residue subjected to flash chromatography (10% EtOAc in hexanes) to afford the deacetylated intermediate (15.6 mg, 87%) as a white solid.

Deacetylated intermediate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66 (q, 6H, J=8.1 Hz), 0.81 (s, 3H), 0.98 (t, 9H, J=7.8 Hz), 1.12 (s, 3H), 1.12–1.19 (m, 1H), 1.37 (s, 3H), 1.74 (s, 3H), 1.70–1.82 (m, 1H), 1.87–1.97 (m, 1H), 2.03–2.14 (m, 1H), 2.39 (d, 1H, J=18.0 Hz), 2.49 (dd, 1H, J=3.1, 18.0 Hz), 2.98 (t, 1H, J=0.9 Hz), 4.11 (s, 2H), 4.27 (dd, 1H, J=2.1, 3.6 Hz).

To a solution of the alcohol (15.6 mg, 42.6 μmol) (described above) in CH_2Cl_2 (3.0 mL) was added a mixture

of $NaHCO_3$ (11.0 mg, 131 μmol) and Dess–Martin periodinane (55.0 mg, 130 μmol). After 2.5 h at rt, the reaction was quenched with 2-propanol, filtered through a pad of silica, concentrated, and the residue purified via flash chromatography (5% EtOAc in hexanes) to afford enal **16** (11.3 mg, 73%) as a white solid.

16: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.56 (q, 6H, *J*=7.8 Hz), 0.80 (s, 3H), 0.94 (t, 9H, *J*=7.8 Hz), 1.17 (s, 3H), 1.15–1.18 (m, 1H), 1.30 (s, 3H), 1.60–1.68 (m, 1H), 2.00 (s, 3H), 1.92–2.11 (m, 2H), 2.56 (s, 2H), 3.03 (t, 1H, *J*=1.0, 2.1 Hz), 4.77 (t, 1H, *J*=2.4 Hz), 10.03 (s, 1H).

4.1.7. Ketone 19. To a solution of the monoacetylated intermediate (see above) (56.2 mg, 191 μmol) in CH_2Cl_2 (15 mL) at rt was added $NaHCO_3$ (70.0 mg, 0.825 mmol) and Dess–Martin periodinane (350.0 mg, 0.825 mmol). After 2 h, the reaction was quenched with 2-propanol, concentrated, and filtered through a silica pad. The residue was subjected to flash chromatography (25% EtOAc in hexanes) to afford **19** (52.4 mg, 94%) as a light tan solid.

19: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.23 (s, 3H), 1.69 (s, 3H), 1.80–1.87 (m, 2H), 1.97 (s, 3H), 2.43 (td, 1H, *J*=4.8, 14.4 Hz), 2.54 (s, 2H), 2.70 (ddd, 1H, *J*=4.0, 7.5, 14.4 Hz), 2.54 (s, 1H), 4.74 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 20.9, 23.4, 26.0, 28.9, 32.8, 34.5, 35.6, 37.4, 53.1, 53.5, 60.9, 67.4, 128.8, 130.6, 170.9, 213.0.

4.1.8. Lactol 20. To a solution of ketone **19** (51.1 mg, 175 μmol) in methanol (5.0 mL) at rt was added a solution of K_2CO_3 (70.0 mg, 506 μmol) in H_2O (1.0 mL). After 20 h, the solution was poured into brine (30 mL) and extracted (CH_2Cl_2, 3×30 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The resulting tan solid (44.2 mg, 99%) was used without further purification.

20: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (s, 3H), 1.19 (s, 3H), 1.22 (s, 3H), 1.46–1.53 (m, 1H), 1.58 (s, 3H), 1.70–1.88 (m, 3H), 2.33 (dd, 1H, *J*=3.0, 17.4 Hz), 2.51 (s, 1H), 2.52 (d, 1H, *J*=17.7 Hz), 3.06 d, 1H, *J*=3.0 Hz), 4.34 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 20.3, 26.4, 29.5, 31.6, 33.9, 34.0, 34.7, 49.6, 50.5, 65.0, 66.5, 106.5, 117.7, 137.4; mass spectrum (EI): *m/e* (%relative intensity) 250 $(M)^+$ (2), 193 (28), 162 (22), 149 (92), 129 (43), 107 (43), 97 (71), 91 (49), 69 (100), 55 (53); *m/e* calcd for $C_{15}H_{23}O_3$ 251.1647; found 251.1650.

4.1.9. Aldehyde 21. To a solution of lactol **20** (21.0 mg, 83.4 μmol) in CH_2Cl_2 (3.0 mL) was added PCC (90.0 mg, 418 μmol). After 16 h at rt, additional PCC (45.0 mg, 209 μmol) was added. After an additional 3 h, the solution was diluted with hexanes (2.0 mL), filtered through a pad of silica, concentrated, and the residue subjected to flash chromatography (1:5 EtOAc/hexanes) to afford the title compound (8.2 mg, 32%) as a white solid and recovered starting material (9.4 mg, 40%).

21: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 3H), 1.39 (s, 3H), 1.78 (s, 3H), 1.81–1.90 (m, 1H), 1.97 (s, 3H), 1.96–2.04 (m, 1H), 2.45 (ddd, 1H, *J*=5.7, 8.1, 15.3 Hz), 2.64 (s, 2H), 2.90 (ddd, 1H, *J*=5.7, 8.7, 15.2 Hz), 3.24 (t, 1H, *J*=2.1 Hz), 10.01 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 23.4, 25.9, 28.1, 33.5, 34.8, 35.2, 37.2, 53.3, 54.4, 68.4, 134.8, 141.5, 191.8, 209.4; IR (film) cm^{-1} 1378, 1420, 1627, 1678, 1712, 1737, 2942, 2966; mass spectrum (EI): *m/e* (%relative intensity) 233 $(M-CH_3)^+$ (29), 205 (8), 189 (12), 175 (80), 161 (27), 147 (36), 133 (100), 119 (65), 105 (81), 91 (48), 77 (44), 55 (73).

4.1.10. Ketone 24. A heterogeneous mixture of enal **21** (4.4 mg, 18 μmol), pyrone **23** (6.0 mg, 22 μmol), Na_2SO_4 (3.0 mg) and piperidinium acetate (1.5 mg, 11 μmol) in dry ethyl acetate (1.5 mL) was sealed in a 3 mL vial and heated to 90°C. After 18 h, the mixture was filtered through a pad of silica, concentrated, and purified by flash chromatography (60% EtOAc in hexanes) to afford the title compound (6.5 mg, 72%) as a bright yellow solid in a diastereomeric ratio of 85:15 with the desired isomer being major.

24: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.18 (s, 3H), 1.54 (s, 3H), 1.56 (s, 3H), 1.65–1.75 (m, 1H), 1.97–2.05 (m, 1H), 2.38–2.42 (m, 2H), 2.78–2.89 (m, 2H), 3.33 (d, 1H, *J*=6.4 Hz), 3.90 (s, 3H), 3.91 (s, 6H), 6.11 (s, 1H), 6.41 (s, 1H), 6.99 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 25.1, 26.7, 28.6, 33.8, 35.6, 36.3, 37.0, 52.4, 52.9, 56.4, 61.0, 66.6, 78.0, 97.1, 102.0, 102.9, 112.8, 126.6, 132.7, 141.2, 147.3, 153.5, 161.3, 163.4, 211.7; IR (film) cm^{-1} 1129, 1504, 1551, 1582, 1717, 2919, 2962; mass spectrum (EI): *m/e* (%relative intensity) 508 $(M)^{+\cdot}$ (43), 493 $(M-CH_3)^+$ (100), 465 (55), 291 (6), 228 (13), 195 (33), 173 (9), 157 (11), 149 (90), 91 (11), 69 (20), 57 (27); *m/e* calcd for $C_{29}H_{32}O_8$ 508.2097; found 508.2090.

4.1.11. Diol 31. A solution of pentacycle **6** (33.5 mg, 70 μmol) in 2 mL CH_2Cl_2 was cooled to −10°C and solid *m*-CPBA (35.5 mg, 77%, 160 μmol) was added along with 5.0 mg of K_2CO_3. The mixture was stirred and allowed to warm to rt over a period of 2 h at which time an additional 15.0 mg of *m*-CPBA was added. An additional 10.0 mg was added after another 5 h along with 5.0 mg of K_2CO_3. Four hours after the final addition, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated $NaHCO_3$ (3×20 mL). The organic layer was then washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was subjected to silica gel flash chromatography (gradient, 0–40% EtOAc in hexanes) to afford 2.9 to 7.6 mg (8–21%) of diol **31** depending on the trial.

31: R_f=0.46 (65% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.18 (s, 3H), 1.25 (m, 1H), 1.48 (s, 3H), 1.54 (s, 3H), 1.70 (m, 1H), 2.01 (m, 1H), 2.43 (d, 1H, *J*=16.8 Hz), 2.81 (ddd, 1H, *J*=7.5, 11.7, 19.2 Hz), 2.99 (dd, 1H, *J*=3.9, 16.8 Hz), 3.48 (d, 1H, *J*=3.9 Hz), 3.92 (s, 3H), 3.94 (s, 3H), 3.95 (s, 1H), 6.11 (s, 1H), 6.92 (d, 1H, *J*=8.6 Hz), 7.36 (d, 1H, *J*=2.1 Hz), 7.53 (dd, 1H, *J*=2.1, 8.6 Hz); mass spectrum (CI): *m/e* (%relative intensity) 513 (10) $(M+H)^+$, 447 (7), 391 (14), 307 (73), 154 (100), 107 (74); *m/e* calcd for $C_{28}H_{33}O_9$ 513.2125; found 513.2130.

4.1.12. Alcohol 33. To a solution of pentacycle **6** (100 mg, 0.21 mmol) in THF (8 mL) was added a 2.0 M solution of $BH_3{\cdot}Me_2S$ in THF (0.52 mL, 1.04 mmol) at −78°C. The reaction mixture was stirred at −78°C for 1 h and warmed to room temperature. The reaction was quenched with H_2O

(10 mL) and the normal aqueous workup was employed. Flash chromatographic separation (gradient, 40–60% EtOAc in hexanes) gave **33** (51.2 mg, 50%) as a yellow solid.

33: R_f=0.20 (66% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75 (s, 3H), 1.16 (s, 3H), 1.39 (s, 3H), 1.42 (s, 3H), 1.46 (td, 1H, *J*=3.5, 13.5 Hz), 1.61 (dt, 1H, *J*=3.5, 14 Hz), 1.74 (brs, 1H), 1.81–1.96 (m, 2H), 2.38 (d, 1H, *J*=17 Hz), 2.78 (dd, 1H, *J*=4, 17 Hz), 3.15 (d, 1H, *J*=4 Hz), 3.93 (s, 3H), 3.95 (s, 3H), 4.27 (dd, 1H, *J*=5, 11 Hz), 6.39 (s, 1H), 6.60 (s, 1H), 6.90 (d, 1H, *J*=8.5 Hz), 7.31 (d, 1H, *J*=2 Hz); 7.39 (dd, 1H, *J*=2.5, 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.4, 25.9, 26.2, 26.3, 27.5, 34.0, 35.6, 36.0, 45.3, 51.5, 56.0, 56.1, 65.2, 72.6, 78.2, 96.4, 101.8, 108.2, 111.0, 111.7, 119.0, 124.2, 137.6, 149.2, 153.5, 159.8, 162.0, 163.5; mass spectrum (CI): *m/e* (% relative intensity) 481 $(M+H)^+$ (100), 261 (10), 195 (9), 165 (26), 135 (12), 119 (30); *m/e* calcd for $C_{28}H_{33}O_7$ 481.2225; found 481.2226.

4.1.13. *meta*-Chlorobenzoate 34. To a solution of alcohol **33** (136.0 mg, 0.28 mmol) in CH_2Cl_2 (6 mL) was added $NaHCO_3$ (238.0 mg, 2.83 mmol) and *m*-CPBA (284.0 mg, 1.14 mmol) sequentially at 0°C. The mixture was stirred over 12 h and was then poured into 25 mL of sat aq NaCl and extracted (CH_2Cl_2, 3×25 mL). The combined extracts were then dried over Na_2SO_4. The crude product was purified by flash chromatography (40% EtOAc in hexanes) to afford **34** (76.4 mg, 41%) as a light yellow solid.

34: R_f=0.22 (66% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.03 (s, 3H), 1.17–1.24 (m, 1H), 1.71–1.77 (m, 1H), 1.75 (s, 3H), 1.77 (s, 3H), 1.81–1.87 (m, 1H), 1.96 (d, 1H, *J*=15.5 Hz), 2.11 (dt, 1H, *J*=2.5, 13.5 Hz), 2.38 (d, 1H, *J*=4 Hz), 2.67 (dd, 1H, *J*=7, 15.5 Hz), 3.69 (s, 1H), 3.94 (s, 3H), 3.96 (s, 3H), 4.66 (brd, 1H, *J*=11 Hz), 5.00 (s, 1H), 5.55 (d, 1H, *J*=7 Hz), 6.33 (s, 1H), 6.91 (d, 1H, *J*=8.5 Hz), 7.30 (d, 1H, *J*=2 Hz), 7.40 (dd, 1H, *J*=2, 8.5 Hz), 7.45 (t, 1H, *J*=8 Hz), 7.59 (ddd, 1H, *J*=1, 2, 8 Hz), 7.87 (td, 1H, *J*=2, 8 Hz), 7.97 (t, 1H, *J*=2 Hz), mass spectrum (CI): *m/e* (% relative intensity) 653 $(M+H)^+$ (100), 315 (15), 277 (16), 261 (13), 203 (12), 165 (48), 139 (89), 119 (36); *m/e* calcd for $C_{35}H_{38}O_{10}Cl$ 653.2154; found 653.2150.

4.1.14. The xanthate. To a solution of *m*-chlorobenzoate **34** (28.0 mg, 43 μmol) in CH_2Cl_2 (3 mL) was added DIBAL-H (1 M in hexanes, 0.2 mL, 0.2 mmol) at −78°C. The reaction mixture was stirred at −78°C for 1 h and then warmed to room temperature. The reaction was quenched with 1 M HCl (10 mL) and extracted (CH_2Cl_2, 3×10 mL). After normal workup, the crude product was purified *via* flash chromatography (gradient, 40–60% EtOAc in hexanes) to give the desired alcohol (14.2 mg, 63%) as a white solid.

The alcohol: R_f=0.20 (66% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.20 (td, 1H, *J*=3, 13.5 Hz), 1.23 (s, 3H), 1.63–1.68 (m, 1H), 1.66 (s, 3H), 1.77–1.83 (m, 1H), 1.80 (s, 3H), 1.87 (d, 1H, *J*=15 Hz), 2.06 (dt, 1H, *J*=2.5, 14 Hz), 2.32 (brs, 1H), 2.52 (dd, 1H, *J*=6.5, 15 Hz), 3.69 (brs, 1H), 3.93 (s, 3H), 3.94 (s, 3H), 4.29 (dd, 1H, *J*=3, 6.5 Hz), 4.58 (dd, 1H, *J*=4.5, 11.5 Hz), 4.92 (s, 1H), 6.32 (s, 1H), 6.90 (d, 1H, *J*=8.5 Hz), 7.28 (d, 1H, *J*=2 Hz), 7.39 (dd, 1H, *J*=2, 8.5 Hz).

The xanthate: To a solution of triol (13.0 mg, 25.0 μmol) in THF (3 mL) was added NaH (60% suspension in mineral oil, 6.0 mg, 150 μmol) at 0°C. After stirring for 30 min, CS_2 (10 μL, 0.16 mmol) was added, and after an additional 30 min, iodomethane (10 μL, 0.16 mmol) was added. The reaction was stirred at room temperature for 2 h and then quenched with H_2O (0.5 mL). After normal workup the crude product was purified by flash chromatography to afford the xanthate (7.9 mg, 52%) as a colorless oil.

The xanthate: R_f=0.31 (66% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00–1.09 (m, 1H), 1.05 (s, 3H), 1.09 (s, 3H), 1.47–1.52 (m, 1H), 1.68 (s, 3H), 1.81 (s, 3H), 2.02–2.09 (m, 2H), 2.15 (d, 1H, *J*=16 Hz), 2.62 (s, 3H), 2.65 (dd, 1H, *J*=7.5, 17 Hz), 3.95 (s, 3H), 3.96 (s, 3H), 5.12 (dd, 1H, *J*=4, 11 Hz), 5.21 (s, 1H), 6.93 (d, 1H, *J*=7 Hz), 7.30 (d, 1H, *J*=2.5 Hz), 7.42 (dd, 1H, *J*=2.5, 8.5 Hz).

4.1.15. Triol 35. Solid LAH (530.0 mg, 3.0 equiv.) was cautiously added to THF (100 mL) at 0°C. The diol **15** (1.17 g, 4.64 mmol) was dissolved in THF (20 mL) and slowly added to the LAH suspension. A condenser was fitted to the flask, the system purged with nitrogen, and the solution heated to reflux overnight. The next day, the reaction was cooled to 0°C and excess hydride destroyed by titration with 1 M HCl. Water (50 mL) was added, and the biphase saturated with NaCl. Extraction with EtOAc (4×35 mL), drying (Na_2SO_4) and evaporation of solvents yielded crude **35** which was purified by silica gel chromatography (50% EtOAc in hexanes) to afford pure **35** (870.0 mg, 74%) as a white solid. Range of the yield for different trials was within 62–90%.

35: mp=135.5–137.5°C; R_f=0.42 (25% acetone in chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.05 (s, 3H), 1.14 (m, 1H), 1.26 (m, 1H), 1.68–1.88 (m, 3H), 2.00–2.14 (m, 3H), 2.18–2.30 (m, 1H), 3.46 (s, 1H), 4.00 (m, 1H), 4.06 (d, 1H, *J*=11.7 Hz), 4.07 (brs, 1H), 4.31 (dd 1H, *J*=7.2, 11.7 Hz), 5.23 (d, 1H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 23.5, 24.6, 25.3, 25.7, 27.7, 28.7, 30.2, 38.0, 46.3, 57.4, 73.4, 78.0, 134.2, 135.5; IR (film) cm^{-1} 3356 brs, 2966 s, 1654 m; mass spectrum (EI): *m/e* (%relative intensity) 236 $(M-H_2O)^+$ (35), 221 (40), 185 (33), 162 (55), 152 (47), 139 (61), 137 (69), 119 (61), 109 (66), 81 (100).

4.1.16. Acetate 36. Triol **35** (650.0 mg, 2.56 mmol) was dissolved in pyridine (30 mL) and acetic anhydride (2.41 mL, 10 equiv.) was slowly added. The solution was allowed to stir at room temperature overnight. Solvent, excess acetic anhydride, and AcOH were removed by vacuum distillation at room temperature to afford **36** (750.0 mg, 99%) as a white solid which was not further purified.

36: mp=134–136°C; R_f=0.55 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.04 (s, 3H), 1.09 (s, 3H), 1.12 (m, 1H), 1.70–1.82 (m, 3H), 1.74 (s, 3H), 1.98–2.07 (m, 2H), 2.08 (s, 3H), 2.32 (ddd, 1H, *J*=9.5, 10.0, 19.0 Hz), 3.81 (d, 1H, *J*=6.0 Hz), 3.97 (s, 1H), 3.99 (br, 1H), 4.63 (d, 1H, *J*=12.5 Hz), 4.97 (d, 1H, *J*=12.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 21.3, 23.8, 25.0, 25.5, 26.0, 28.2, 29.8, 30.5, 38.4, 46.4, 61.3, 73.5, 84.0, 130.4, 139.1,

170.8; IR (film) cm^{-1} 3381 br, 2992 s, 1731 vs; mass spectrum (EI): *m/e* (%relative intensity) 236 $(M-AcOH)^+$ (43), 221 (59), 185 (51), 162 (76), 152 (77), 139 (100), 137 (79), 119 (75), 109 (85), 91 (47), 81 (97).

4.1.17. Ketone 38. Acetate **36** (1.45 g, 4.9 mmol) was dissolved in CH_2Cl_2 (60 mL) along with NMO (860.0 mg, 1.5 equiv.) and powdered 4 Å molecular sieves (0.50 g). TPAP (85.0 mg, 0.050 equiv.) was added, and the mixture stirred overnight. The mixture was then transferred onto a silica gel column loaded with CH_2Cl_2 and eluted until all of the reaction mixture was on the column. The solvent was then changed to $CHCl_3$ and fractions were collected until the product had eluted. Removal of solvent under vacuum gave pure **38** (1.44 g, 4.9 mmol, 100%) as a white solid.

38: mp=153–154°C; R_f=0.53 (50% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.22 (s, 3H), 1.50 (s, 3H), 1.65 (ddd, 1H, *J*=2.4, 6.6, 12.3 Hz), 1.69 (s, 3H), 1.72 (ddd, 1H, *J*=1.1, 7.2, 13.5 Hz), 1.90 (ddd, 1H, *J*=6.6, 11.4, 18 Hz), 2.02 (s, 3H), 2.08–2.28 (m, 4H), 2.90 (ddd, 1H, *J*=6.6, 14.7, 15.0 Hz), 4.53 (d, 1H, *J*=13.2 Hz), 4.92 (d, 1H, *J*=12.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 21.2, 23.6, 23.7, 25.3, 27.0, 28.8, 35.9, 38.0, 38.7, 60.4, 63.5, 80.7, 129.8, 137.4, 171.2, 213.9; IR (film) cm^{-1} 3527 m, 3387 m, 2942 m, 1722 vs, 1703 s; mass spectrum *m/e* (% relative intensity): 234 (100), 219 (41), 201 (34), 191 (26), 178 (36), 163 (48), 161 (46), 146 (48), 136 (89), 119 (49).

4.1.18. Lactol. Ketone **38** (1.83 g, 6.27 mmol) was dissolved in MeOH/H_2O/THF (2:1:1, 50 mL) and powdered K_2CO_3 (2.50 g, 3.0 equiv.) was added. The solution was stirred overnight. Water (50 mL) was added and the solution extracted (EtOAc, 5×25 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). Removal of solvents under vacuum yielded the lactol (1.49 g, 94%) as a white solid which was determined to need no further purification.

Lactol: mp=147.5–148.5; R_f=0.22 (50% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 1.01 (s, 6H), 1.13–1.18 (m, 1H), 1.16 (s, 3H), 1.45 (s, 3H), 1.56 (s, 1H), 1.64 (ddd, 1H, *J*=3.0, 4.5, 13.5 Hz), 1.68–1.86 (m, 3H), 1.98–2.02 (m, 1H), 2.06 (brdd, 1H, *J*=6.0, 19.0 Hz), 2.22 (brdd, 1H, *J*=10.5, 18.0 Hz), 2.70 (s, 1H), 4.25 (brd, 1H, *J*=13.0 Hz), 4.52 (brd, 1H, *J*=13.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 23.4, 25.5, 26.9, 27.5, 28.4, 30.2, 31.6, 34.0, 38.3, 65.0, 75.8, 106.6, 122.8, 135.4; IR (film) cm^{-1} 3422br, 2949 s, 1648w; mass spectrum (EI): *m/e* (% relative intensity) 252 M^+ (2), 234 $(M-H_2O)^+$ (16), 149 (25), 138 (100), 123 (43), 109 (52).

4.1.19. Aldehyde 37-α. The lactol from the previous step (300.0 mg, 1.19 mmol) was dissolved in CH_2Cl_2 (50 mL) and PCC (1.03 g, 4 equiv.) was added. The solution turned black, and was stirred overnight. The heterogeneous mixture was filtered through silica gel, and eluted with EtOAc/hexanes (1:1). Evaporation of all but 2 mL of solvent followed by exposure of the remaining solution to low vacuum (ca. 100 mmHg) gave **37**-α (232.0 mg, 78%) as clear prisms which were washed with hexanes.

37-α: mp=162–164°C; R_f=0.21 (50% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 3H), 1.16 (s, 3H), 1.17 (s, 3H), 1.42 (s, 1H), 1.52 (ddd, 1H *J*=5.0, 5.0, 14.0 Hz), 1.77 (ddd, 1H, *J*=8.0, 9.5, 18.0 Hz), 1.95 (ddd, 1H, *J*=4.0, 13.5, 13.5 Hz), 2.12 (ddd, 1H, *J*=2.0, 8.0, 14.5 Hz), 2.18 (s, 3H), 2.34 (ddd, 1H, *J*=4.0, 4.0, 12.0 Hz), 2.46–2.63 (m, 3H), 10.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.5, 20.2, 24.7, 26.5, 27.8, 34.5, 37.8, 39.4, 39.8, 54.0, 81.3, 139.2, 158.4, 189.9, 212.7; IR (film) cm^{-1} 3488 brs, 2950 m, 1707 vs, 1665 vs; mass spectrum (EI): *m/e* (%relative intensity) 250 M^+ (37), 217 (24), 181 (36), 152 (100), 138 (40), 123 (49), 109 (34), 55 (44).

4.1.20. Ketone 39-AB-*cis*. Enal **37**-α (100.0 mg, 0.40 mmol) was placed in a sealed tube along with EtOAc (4 mL), Na_2SO_4 (100.0 mg), pyrone **8** (197.0 mg, 2.0 equiv.), and piperidinium HCl (42.0 mg, 1 equiv.). The mixture was heated to 150°C for 5 d. Removal of solvent, followed by filtration through silica gel (50% EtOAc in hexanes), followed by flash silica gel chromatography (10% acetone in CH_2Cl_2) afforded **39**-*cis* (57.0 mg, 30%) as a yellow solid.

39-AB-*cis*: mp=188–190°C; R_f=0.39 (67% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (s, 3H), 1.10 (s, 3H), 1.31 (s, 3H), 1.45 (s, 3H), 1.49 (s, 1H), 1.61–1.73 (m, 3H), 2.04 (ddd, 1H, *J*=4.5, 8.5, 14.0 Hz), 2.13 (m, 1H), 2.23 (ddd, 1H, *J*=4.5, 9.5, 18.5 Hz), 2.40 (ddd, 1H, *J*=7.0, 7.0, 17.0 Hz), 2.64 (ddd, 1H, *J*=7.5, 7.5, 17.0 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 6.01 (s, 1H), 6.33 (s, 1H), 6.84 (d, 1H, *J*=8.5 Hz), 7.24 (d, 1H, *J*=2.5 Hz), 7.34 (dd, 1H, *J*=2.5, 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.0, 24.0, 26.1, 26.9, 30.2, 33.2, 33.4, 35.9, 38.9, 56.1, 56.2, 58.1, 78.9, 80.7, 96.1, 100.9, 108.3, 111.1, 114.3, 119.2, 124.0, 135.8, 149.3, 151.6, 160.6, 161.4, 163.0, 212.0; IR (film) cm^{-1} 3484 brs, 2960 m, 1704 vs, 1625 m, 1515 vs. mass spectrum (CI): *m/e* (%relative intensity) 480 (67), 465 (22), 446 (25), 437 (13), 327 (49), 261 (24), 165 (100), 137 (12); *m/e* calcd for $C_{28}H_{32}O_7$ 480.2148; found 480.2143.

4.1.21. Ketone 40-AB-*trans*. Pentacycle **42** (see below) (100.0 mg, 0.21 mmol) was dissolved in CH_2Cl_2 (2 mL) and NMO (36.0 mg, 1.50 equiv.) was added. TPAP (4.0 mg, 0.050 equiv.) was then added and the reaction was allowed to stir at room temperature for two h. The solution was loaded onto a short silica gel column and eluted with $CHCl_3$. Evaporation of solvent gave the ketone (96 mg, 95%) as a yellow solid which formed needles when crystallized by slow evaporation from CH_2Cl_2.

40-AB-*trans*: mp=228–230°C (dec.); R_f=0.14 (50% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.20 (s, 3H), 1.55 (s, 3H), 1.66 (s, 3H), 1.71 (ddd, 1H, *J*=6.0, 7.5, 14.0 Hz), 1.84 (ddd, 1H, *J*=3.0, 5.0, 14.5 Hz), 1.98 (ddd, 1H, *J*=4.0, 14.0, 14.0 Hz), 2.03 (m, 1H), 2.08 (ddd, 1H, *J*=5.0, 10.0, 15.0 Hz), 2.33 (ddd, 1H, *J*=5.0, 14.0, 14.0 Hz), 2.63 (ddd, 1H, *J*=5.5, 6.5, 14.0 Hz), 2.83 (ddd, 1H, *J*=5.5, 10.0, 14.5 Hz), 3.95 (s, 3H), 3.96 (s, 3H), 6.38 (s, 1H), 6.92 (d, 1H, *J*=8.5 Hz), 7.32 (d, 1H, *J*=2.0 Hz), 7.42 (dd, 1H, *J*=2.0, 8.0 Hz), 7.47 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 26.0, 26.9, 27.6, 28.2, 33.9, 36.6, 37.3, 37.9, 56.2, 56.3, 57.3, 79.3, 79.7, 96.3, 101.0, 108.4, 111.2, 119.3, 119.6, 124.3, 134.1, 149.4, 151.6, 160.6, 161.9, 162.7, 211.3; IR (film) cm^{-1} 2926 m, 1711 vs,

1602 m, 1514 vs; mass spectrum (CI): *m/e* (%relative intensity) 481 $(M+H)^+$ (100), 463 $(M+H^+-H_2O)^+$ (10), 87 (55), 84 (43), 74 (67), 73 (22); *m/e* calcd for $C_{28}H_{32}O_7$ 480.2143; found 480.2155.

4.1.22. Aldehyde 41. Triol **35** (1.55 g, 6.09 mmol) was dissolved in CH_2Cl_2 (40 mL) and 4 Å molecular sieves (powdered, 200.0 mg) were added. TPAP (107.0 mg, 0.050 equiv.) was added. The reaction was stirred at room temperature for 30 min at which time TLC (vanillin) indicated consumption of starting material. The solution was loaded onto a silica gel column and eluted with $CHCl_3$. Evaporation of solvent provided enal **41** (1.07 g, 70%) as an unstable yellow syrup.

41: R_f=0.49 (25% acetone in chloroform); ^{1}H NMR δ 1.03 (s, 6H), 1.18 (s, 3H), 1.70–1.82 (m, 4H), 2.00–2.18 (m, 2H), 2.13 (s, 3H), 2.25 (ddd, 1H, *J*=2.5, 5.0, 14.0 Hz), 2.53 (ddd, 1H, *J*=9.0, 9.0, 20.5 Hz), 3.16 (d, 1H, *J*=5.0 Hz), 4.41 (s, 1H), 4.80 (m, 1H), 10.20 (s, 1H); ^{13}C NMR δ 19.3, 23.2, 24.5, 25.1, 26.2, 28.0, 30.2, 32.5, 35.1, 38.4, 72.0, 85.1, 138.8, 159.6, 194.6; IR (film) cm^{-1} 3380 brs, 2944 vs, 1754 s, 1666 vs, 1450 s; mass spectrum (EI): *m/e* (%relative intensity) 234 $(M-H_2O)^+$ (100), 206 (7), 149 (54), 135 (52), 91 (48).

4.1.23. Diol 42. Enal **41** (155.0 mg, 0.62 mmol) was dissolved in EtOAc (4 mL) and placed in a sealed tube along with Na_2SO_4 (200.0 mg), piperidinium acetate (89.0 mg, 1.0 equiv.), and pyrone **8** (154.0 mg, 1.0 equiv.). The vessel was sealed under nitrogen and placed in a 70°C oil bath for 2 h. Solvent was removed in vacuo and the crude ^{1}H NMR spectrum indicated a diastereomeric ratio in excess of 15:1 favoring the desired isomer. The residue was filtered through silica gel (50% EtOAc in hexanes) to afford impure **42** which was further purified by flash chromatography (10% acetone in CH_2Cl_2) to afford the pure **42** (149.0 mg, 50%) as a yellow solid.

42: mp=163–165°C; R_f=0.24 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.04 (s, 3H), 1.31 (s, 3H), 1.53 (s, 3H), 1.76 (ddd, 1H, *J*=2.5, 4.0, 12.0 Hz), 1.82–1.87 (m, 2H), 1.94 (ddd, 1H, *J*=3.0, 4.5, 13.0 Hz), 2.07 (ddd, 1H, *J*=3.5, 14.0, 14.0), 2.19 (m, 1H), 2.56 (dddd, 1H, *J*=1.0, 5.5, 6.0, 6.0), 2.96 (brd, 1H, *J*=14.5 Hz), 3.94 (s, 3H), 3.95 (s, 3H), 4.36 (d, 1H, *J*=3.0 Hz), 4.55 (brd, 1H, *J*=6.5 Hz), 6.42 (s, 1H), 6.45 (s, 1H), 6.91 (d, 1H, *J*=8.5 Hz), 7.28 (d, 1H, *J*=1.5 Hz), 7.41 (dd, 1H, *J*=2.0, 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0, 24.3, 25.1, 27.8, 27.9, 28.1, 30.6, 31.1, 34.5, 38.5, 47.5, 56.2, 56.3, 72.1, 80.7, 96.7, 100.8, 108.2, 111.2, 111.3, 119.2, 124.2, 142.4, 149.3, 151.5, 160.0, 162.4, 162.8; IR (film) cm^{-1} 3378 brs, 3087 mw, 2930 s, 1693 s, 1682 s; mass spectrum (CI): *m/e* (%relative intensity) 483 $(M+H)^+$ (9), 466 (7), 465 $(M+H-H_2O)^+$ (43), 101 (17), 87 (100), 74 (20), 73 (35), 65 (40); *m/e* calcd for $C_{28}H_{34}O_7$ 482.2299; found 482.2306.

4.1.24. Diol 43. Pyrone **40**-AB-*trans* (37.0 mg, 77.0 μmol) was added to a solution of tetra-*N*-methyl ammonium triacetoxyborohydride (10.0 equiv.) in AcOH (0.5 mL). After 30 min, the reaction was poured into water (5 mL) and extracted with $CHCl_3$ (3×5 mL). The combined organic extracts were washed successively with 0.5 M NaOH (5 mL) and brine (5 mL). The solution was dried (Na_2SO_4) and solvent removed to give crude **43** which was filtered through silica to afford pure **43** (35.0 mg, 94%) as a yellow solid.

43: mp=220–221°C (dec.); R_f=0.29 (2:1 EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.02 (s, 3H), 1.19 (td, 1H, *J*=3, 14 Hz), 1.34 (s, 3H), 1.58 (s, 3H), 1.65 (s, 1H), 1.71 (brs, 1H), 1.72–1.82 (m, 3H), 1.93–2.00 (m, 2H), 2.08 (ddd, 1H, *J*=2, 5, 13.5 Hz), 2.34 (dt, 1H, *J*=5.5, 13.5 Hz), 3.93 (s, 3H), 3.95 (s, 3H), 4.37 (dd, 1H, *J*=6, 9.5 Hz), 6.34 (s, 1H), 6.90 (d, 1H, *J*=8.5 Hz), 7.02 (s, 1H), 7.29 (d, 1H, *J*=2 Hz), 7.39 (dd, 1H, *J*=2, 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 23.6, 24.6, 27.1, 28.2, 28.9, 34.6, 35.6, 37.9, 49.9, 56.0, 56.2, 71.7, 80.9, 81.2, 96.2, 99.7, 108.2, 111.0, 114.8, 119.0, 124.2, 140.5, 149.2, 151.4, 160.0, 161.9, 162.5; IR (film) cm^{-1} 3496 brs, 2936 m, 1694 s, 1611 m, 1534 s, 1515 vs; mass spectrum (CI): *m/e* (%relative intensity) 483 $(M+H)^+$ (100), 465 $(M+H-H_2O)^+$ (18), 447 $(M+H-2H_2O)^+$ (4), 181 (7), 65 (4); *m/e* calcd for $C_{28}H_{34}O_7$ 482.2299; found 482.2311.

4.1.25. Tetraol 44. Diol **43** (42.0 mg, 87.0 μmol) was dissolved in pyridine (0.25 mL) and solid OsO_4 (33.0 mg, 1.50 equiv.) was added. The solution was stirred for 3 h at which time TLC indicated consumption of starting material. Saturated $NaHSO_3$ (100 μL) was then added and the solution was stirred for an additional 3 h. The mixture was then filtered through celite to remove precipitate and the celite was rinsed several times with EtOAc. The water layer was then saturated with NaCl. Extraction (EtOAc, 10×5 mL) followed by drying (Na_2SO_4) and evaporation of solvent afforded a brown tar which was purified by flash chromatography (gradient, 60–90% EtOAc in hexanes) to afford **44** (37.0 mg, 83%) as a white solid.

44: R_f=0.10 (2:1 EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (s, 3H), 1.03 (s, 3H), 1.13 (ddd, 1H, *J*=3, 4.5, 13.5 Hz), 1.14 (s, 3H), 1.46 (s, 3H), 1.70–1.91 (m, 5H), 2.07 (ddd, 1H, *J*=4.5, 13.5, 13.5 Hz), 2.55 (dt, 1H, *J*=4.5, 14 Hz), 3.94 (s, 6H), 4.37 (dd, 1H, *J*=5.5, 11 Hz), 4.82 (brs, 1H), 5.15 (s, 1H), 5.76 (brs, 1H), 6.39 (s, 1H), 6.92 (d, 1H, *J*=8.5 Hz), 7.28 (d, 1H, *J*=2 Hz), 7.41 (dd, 1H, *J*=2, 8.5 Hz); mass spectrum (CI): *m/e* (%relative intensity) 515 $(M-H)^-$ (100), 497 $(M-H_2O-H)^-$ (10), 275 (9).

4.1.26. Product of triethylsilane/TFA and 44. Alcohol **44** (8.0 mg, 16.0 μmol) was dissolved in CH_2Cl_2 (50 μL) and triethylsilane (50 μL). TFA (2 drops) was added, and the solution stirred at room temperature for 2 h. Removal of solvent under high vacuum afforded a tan solid which was purified by PTLC (2:1 EtOAc in hexanes) to afford the hexacycle as the only observed product.

Hexacycle: R_f=0.18 (2:1 EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (s, 3H), 0.95 (s, 3H), 1.24 (td, 1H, *J*=3, 13.5 Hz), 1.28 (s, 3H), 1.65 (s, 3H), 1.68 (m, 1H), 1.73–1.87 (m, 4H), 2.00–2.07 (m, 2H), 2.42 (br, 1H), 3.63 (br, 1H), 3.93 (s, 3H), 3.94 (s, 3H), 4.60 (dd, 1H, *J*=5, 12 Hz), 4.90 (s, 1H), 6.30 (s, 1H), 6.89 (d, 1H, *J*=8.5 Hz), 7.27 (d, 1H, *J*=2 Hz), 7.38 (dd, 1H, *J*=2, 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 23.8, 24.4, 26.1, 26.5, 26.6, 30.7,

35.7, 36.5, 50.2, 56.2, 56.4, 71.2, 73.6, 80.1, 84.2, 88.7, 96.4, 98.5, 108.6, 111.2, 119.4, 124.2, 149.4, 151.7, 160.9, 163.8, 164.2; IR (film) cm^{-1} 3390 br, 2943 m, 1694 s, 1632 m, 1572 s, 1516 vs; mass spectrum (CI): *m/e* (%relative intensity) 497 $(M-H)^-$ (100), 291 (1); *m/e* calcd for $C_{28}H_{34}O_8$ 498.2248; found 498.2252.

4.1.27. Acetate 45. Alcohol **44** (30.0 mg, 62.2 μmol) was dissolved in Ac_2O and 10% Pd on carbon (10.0 mg) was added. The flask was evacuated and filled with hydrogen from a balloon. The mixture was stirred for 3 h, at which time TLC indicated consumption of starting material. Filtration through celite to remove catalyst followed by distillation of solvent afforded a crude mixture (10:1 by ^1H NMR) of **45** and triol **47**. Flash chromatography (gradient, 50–80% EtOAc in hexanes) afforded **45** (32.0 mg, 93%) as a white solid.

Note that **45** was prepared quantitatively from **44** using Ac_2O and DMAP in pyridine/CH_2Cl_2 at rt via standard work up and purification.

45: R_f=0.36 (2:1 EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.05 (s, 3H), 1.09 (td, 1H, *J*=3, 14 Hz), 1.25 (s, 3H), 1.46 (s, 3H), 1.65 (m, 1H), 1.73 (td, 1H, *J*=3, 13.5 Hz), 1.81 (ddd, 1H, *J*=3.5, 4, 15 Hz), 1.91 (dt, 1H, *J*=4, 14 Hz), 2.04–2.14 (m, 2H, 2.06 (s, 3H), 2.56 (dt, 1H, *J*=3.5, 13 Hz), 3.93 (s, 3H), 3.94 (s, 3H), 4.63 (s, 1H), 5.00 (s, 1H), 5.03 (brs, 1H), 5.39 (dd, 1H, *J*=5.5, 10 Hz), 6.38 (s, 1H), 6.51 (s, 1H), 6.92 (d, 1H, *J*=8.5 Hz), 7.26 (d, 1H, *J*=2 Hz), 7.39 (dd, 1H, *J*=2, 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.9, 22.1, 22.9, 24.5, 25.1, 25.9, 27.3, 30.2, 33.9, 39.1, 48.2, 56.2, 56.3, 62.0, 72.1, 78.5, 80.0, 83.7, 97.1, 100.2, 108.5, 111.3, 119.5, 123.6, 134.7, 149.5, 152.0, 164.5, 165.4, 170.9; IR (film) cm^{-1} 3389 brs, 2951 m, 1724 s, 1680 s, 1634 m, 1516 vs, 1463 s; mass spectrum (CI): *m/e* (%relative intensity) 557 $(M-H)^-$ (100), 539 $(M-H-H_2O)^-$ (3), 497 $(M-H-AcOH)^-$ (24), 479 $(M-H-H_2O-AcOH)^-$ (22); *m/e* calcd for $C_{30}H_{38}O_{10}Na$ 581.2363; found 581.2381.

4.1.28. Acetate 46. Triol **45** (37.0 mg, 66.0 μmol) was dissolved in CH_2Cl_2 (200 μL) and triethylsilane (200 μL). Trifluoroacetic acid (6 drops) was added, and the reaction stirred for 3 h. Removal of all solvent and acid was accomplished by exposure to high vacuum for 30 min to afford a tan solid. Purification by flash chromatography (1:1 EtOAc in hexanes) afforded **46** (32.0 mg, 89%) as a white solid.

46: R_f=0.37 (2:1 EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.09 (s, 3H), 1.21 (m, 1H), 1.30 (s, 3H), 1.45 (s, 1H), 1.72–1.82 (m, 4H), 1.89 (dt, 1H, *J*=4.5, 15 Hz), 1.96 (ddd, 1H, *J*=5, 8, 12.5 Hz), 2.09 (dt, 1H, *J*=5, 13.5 Hz), 2.18 (s, 3H), 2.41 (dt, 1H, *J*=4, 13.5 Hz), 2.44 (d, 1H, *J*=17.5 Hz), 2.91 (d, 1H, *J*=18 Hz), 3.92 (s, 3H), 3.93 (s, 3H), 4.11 (s, 1H), 4.63 (s, 1H), 5.79 (dd, 1H, *J*=5.5, 11.5 Hz), 6.33 (s, 1H), 6.91 (d, 1H, *J*=8 Hz), 7.28 (d, 1H, *J*=2 Hz), 7.37 (dd, 1H, *J*=2, 8 Hz); ^{13}C NMR (1245 MHz, $CDCl_3$) δ 17.0, 22.0, 24.2, 24.6, 24.7, 25.5, 27.2, 29.1, 29.4, 34.5, 39.0, 47.7, 56.0, 56.1, 73.0, 77.4, 81.0, 81.7, 96.5, 97.5, 108.2, 111.1, 118.8, 124.2, 149.2, 151.2, 158.8, 162.5, 164.4, 171.1; IR (film) cm^{-1} 3375 brs, 2952 m, 2927 m, 1737 vs, 1677 vs, 1574 m, 1516 vs; mass spectrum (CI): *m/e* (%relative intensity) 543 $(M+H)^+$ (24), 525 $(M+H-H_2O)^+$ (100), 507 $(M+H-2H_2O)^+$ (16), 483 $(M+H-AcOH)^+$ (66), 465 $(M+H-H_2O-AcOH)^+$ (37), 447 $(M+H-2H_2O-AcOH)^+$ (11), 289 (12), 261 (21); *m/e* calcd for $C_{30}H_{39}O_9$ 543.2594; found 543.2610.

4.1.29. Triol 47. Acetate **46** (30.0 mg, 55.0 μmol) was dissolved in THF (0.5 mL) and MeOH (0.5 mL). Powdered K_2CO_3 (10.0 equiv.) was added, and the reaction stirred at room temperature for 3 h at which time TLC indicated consumption of starting material. Most of the solvent was removed in vacuo and the resulting suspension was purified via SiO_2 chromatography (gradient, 50–100% EtOAc in hexanes) to afford the triol **47** (25.0 mg, 90%) as a white solid.

47: R_f=0.12 (2:1 EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.05 (s, 3H), 1.15 (m, 1H), 1.17 (s, 3H), 1.44 (s, 3H), 1.65–1.81 (m, 4H), 1.87 (dt, 1H, *J*=3.5, 14.5 Hz), 2.03 (dt, 1H, *J*=5.5, 14 Hz), 2.41 (dt, 1H, *J*=5, 14 Hz), 2.89 (d, 1H, *J*=18 Hz), 3.22 (d, 1H, *J*=18 Hz), 3.92 (s, 3H), 3.93 (s, 3H), 4.56 (brs, 1H), 4.64 (dd, 1H, *J*=5.5, 11 Hz), 4.70 (brs, 1H), 6.30 (s, 1H), 6.88 (d, 1H, *J*=9 Hz), 7.24 (d, 1H, *J*=1.5 Hz), 7.33 (dd, 1H, *J*=2, 8.5 Hz); IR (film) cm^{-1} 3349 brs, 2943 m, 1678 s, 1640 m, 1571 s, 1515 vs; mass spectrum (CI): *m/e* (%relative intensity) 501 $(M+H)^+$ (100), 483 $(M+H-H_2O)^+$ (24), 465 $(M+H-2H_2O)^+$ (9), 181 (6); *m/e* calcd for $C_{28}H_{36}O_8$ 500.2405; found 500.2415.

4.1.30. Ketone 48. Triol **47** (22.0 mg, 44.0 μmol) was dissolved in $CHCl_3$ (0.5 mL) along with NMO (8.0 mg, 1.50 equiv.) and TPAP (2.0 mg). The solution was stirred at room temperature for 2 h at which time TLC indicated complete conversion. The solution was loaded onto a SiO_2 column packed in CH_2Cl_2. When all of the reaction solution was loaded, the column was eluted with 5% acetone in $CHCl_3$ to afford **48** (20.0 mg, 90%) as a white solid.

48: R_f=0.33 (2:1 EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.25 (s, 3H), 1.43 (s, 3H), 1.51 (s, 3H), 1.68–1.97 (m, 4H), 2.21 (ddd, 1H, *J*=6, 10.2, 20 Hz), 2.35–2.48 (m, 2H), 2.84 (d, 1H, *J*=17.7 Hz), 2.89 (ddd, 1H, *J*=6.9, 10.2, 15.9 Hz), 3.24 (d, 1H, *J*=17.7 Hz), 3.93 (s, 3H), 3.94 (s, 3H), 4.12 (s, 1H), 6.05 (s, 1H), 6.36 (s, 1H), 6.91 (d, 1H, *J*=8.4 Hz), 7.29 (d, 1H, *J*=2.1 Hz), 7.39 (dd, 1H, *J*=2.1, 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 24.0, 25.9, 26.4, 27.1, 27.9, 28.7, 35.4, 37.4, 38.7, 56.0, 56.1, 57.9, 74.1, 77.2, 79.8, 81.8, 83.2, 96.7, 108.2, 111.1, 118.8, 124.3, 149.2, 155.5, 158.8, 164.6, 216.0; IR (film) cm^{-1} 3495 brs, 3377 brs, 2964 m, 1713 s, 1694 s, 1640 m, 1578 s, 1519 vs; mass spectrum (CI): *m/e* (%relative intensity) 497 $(M-H)^-$ (100), 479 $(M-H-H_2O)^-$ (8); *m/e* calcd for $C_{28}H_{34}O_8$ 498.2248; found 498.2239.

4.1.31. (±)-Arisugacin A (1). A 0.417 M solution of Schlosser's base was prepared by combining THF (5 mL), potassium *tert*-butoxide (281.0 mg) and diisopropyl amine (0.36 mL). The mixture was cooled to −78°C, and *n*-butyl lithium (1.00 mL, 2.5 M in hexanes) was added. The solution was stirred for 30 min, used for the deprotonation

immediately, and then discarded. Ketone **48** (4.0 mg, 8.0 μmol) was dissolved in THF (200 μL) with HMPA (30 μL). The solution was cooled to −78°C and the previously described solution of Schlosser's base (290 μL, 15.0 equiv.) was added. The solution was stirred at −78°C for 20 min and then allowed to warm to room temperature. When room temperature was achieved, the solution was again cooled to −78°C and solid phenylselenyl bromide (9.0 mg, 5.0 equiv.) was added. The solution was maintained at −78°C for 20 min, and then allowed to warm while stirring an additional 1 h. The reaction was quenched with 0.5 M HCl and extracted with EtOAc. Drying of extracts and evaporation, followed by purification on a pipette column (1:1 EtOAc in hexanes) afforded the selenide as a white solid. The phenyl selenide was then dissolved in THF (200 μL) and AcOH (40 μL). The solution was cooled to 0°C and 30% hydrogen peroxide (5 μL) was added. The solution was allowed to warm to room temperature and stir. After 60 min, TLC indicated complete conversion. The reaction was poured into saturated $NaHCO_3$ (1 mL) and extracted with $CHCl_3$ (2×1 mL). The solvent was dried and removed. The residue was purified by pipette column (1:1 EtOAc in hexanes) to afford (±)-arisugacin A (2.7 mg, 67% for 2 steps) as a white solid.

The synthetic sample has an identical R_f value with the natural sample in three different solvent systems: a. 2:1 EtOAc/hexanes: R_f=0.27; b. 2:1 ether/hexanes R_f=0.09; c. 1:9 acetone/chloroform R_f=0.24. In addition, the ^1H NMR of the synthetic sample was unchanged by addition of (+)-arisugacin.

(±)-Arisugacin A: R_f=0.27 (2:1 EtOAc in hexanes); ^1H NMR (500 MHz, pyridine-d_5) δ 1.19 (s, 3H), 1.30 (s, 3H), 1.46 (s, 3H), 1.50 (s, 3H), 1.86–1.98 (m, 3H), 2.90 (dt, 1H, J=4.5, 13.5 Hz), 3.17 (d, 1H, J=17.5 Hz), 3.77 (s, 3H), 3.78 (s, 3H), 4.35 (d, 1H, J=17.5 Hz), 5.95 (d, 1H, J=10.5 Hz), 6.28 (d, 1H, J=10 Hz), 6.79 (s, 1H), 7.00 (d, 1H, J=9 Hz), 7.48 (d, 1H, J=2 Hz), 7.59 (m, 1H), 7.69 (s, 1H), 8.95 (s, 1H); ^{13}C NMR (75 MHz, pyridine-d_5) δ 22.4, 23.9, 24.2, 26.2, 26.5, 27.9, 29.9, 43.2, 56.3 (2C), 56.9, 76.6, 79.5, 81.8, 97.7, 98.3, 109.5, 112.6, 119.5, 124.6, 125.3, 150.0, 152.4, 153.5, 159.0, 163.6, 164.4, 202.6; IR (film) cm^{-1} 3357 brs, 2198 m, 1683 s, 1638 s, 1575 s, 1518 vs; mass spectrum (CI): *m/e* (%relative intensity) 495 $(M-H)^-$ (100), 477 $(M-H-H_2O)^-$ (7), 381 (95), 366 (4); *m/e* calcd for $C_{28}H_{33}O_8$ 497.2170; found 497.2181.

4.2. Supporting information

Experimental procedures as well as NMR spectral, characterization data, and X-ray data are given for all new compounds.

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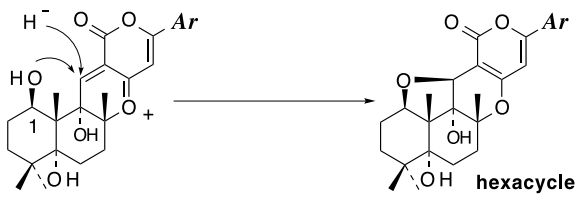
27. When using various peroxyacids, the best result gave the tentatively assigned hexacycle (Ref. 28) as the major product in 28% yield with the desired product in only 21% yield unlike those reported (Ref. 16).
28. The hexacycle was likely a result of intramolecular trapping of the incipient oxocarbenium intermediate by the C1–OH. Such facile trapping by oxygen nucleophiles agrees well with our previous experience in the model studies and with the hexacycle that at this point is not useful for the arisugacin synthesis



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