

Total Synthesis of Coraxeniolide-A

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The first total synthesis of optically active coraxeniolide-A (**1a**) and 4-*epi*-coraxeniolide-A (**1b**) is described. The approach is highly stereoselective and flexible in the preparation of a wide variety of members of the xeniolide family. The use of the Grob-fragmentation was pivotal for the stereospecific elaboration of the nine-membered ring. Coraxeniolide-A (**1a**) was synthesized in 28 steps by using the Hajos–Parrish diketone **2** as starting material which is available enantiomerically pure.

Introduction

The last couple of decades has seen a dramatic increase in the number of highly bioactive natural products isolated from marine organisms.¹ Among these, a new class of diterpenes, the xenicanes, was discovered which exhibit interesting biological properties ranging from cytotoxicity to antitumor activity.² No biosynthetic studies have been performed on xenicanes but it is generally believed that they derive from geranylgeraniol diphosphate via transannular carbocation cyclization in analogy to the series of the caryophyllenes and related compounds.³ They are also postulated to be the precursors to a variety of other cyclic terpenoids.⁴

Coraxeniolide-A (**1a**), a xenicanes which belongs to the xeniolide subclass, was isolated by Scheuer and co-workers in 1981 from a pink coral, *Corallium* sp., as the most abundant constituent in about 650 mg/kg animal.⁵ Structural key features include a nine-membered ring, containing a *E*-double bond and an exocyclic methylene function, reminiscent to the structure of the caryophyllenes, discovered in clove oil and other essential oils. They also possess an α -substituted δ -lactone functionality which is trans-fused to the nine-membered ring. The present study reports the first total synthesis of coraxeniolide-A (**1a**) and 4-*epi*-coraxeniolide-A (**1b**) (Figure 1). Synthetic efforts toward the total synthesis of xeniolides have already been reported by Jung and co-workers.⁶

Results and Discussion

Retrosynthetic Analysis. Our approach was based on previous work of the total synthesis of caryophyllene by Corey and co-workers⁷ (Scheme 1). We planned the

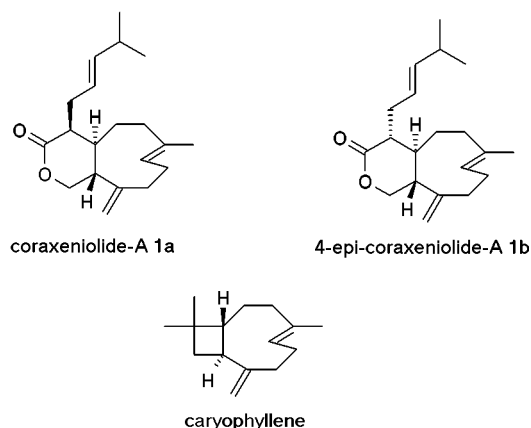
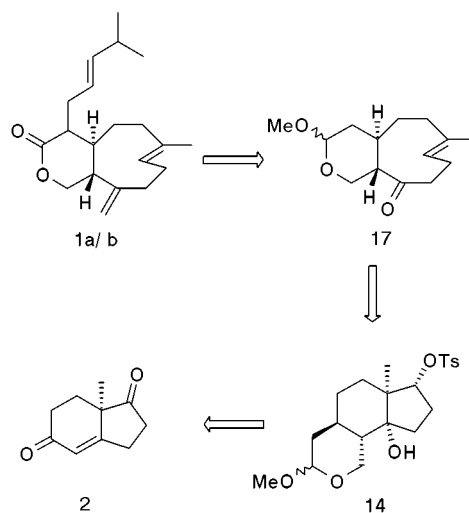


Figure 1.

Scheme 1. Retrosynthetic Analysis



introduction of the side chain at C(4) via ester enolate chemistry as the final step in order to have easy access to other xeniolides. We envisioned a Grob-fragmentation to elaborate the nine-membered ring in a stereospecific manner as a key step of the synthesis. Thus, tosylate **14** was regarded as a potential key intermediate. As starting material we chose the Hajos–Parrish diketone **2**, which

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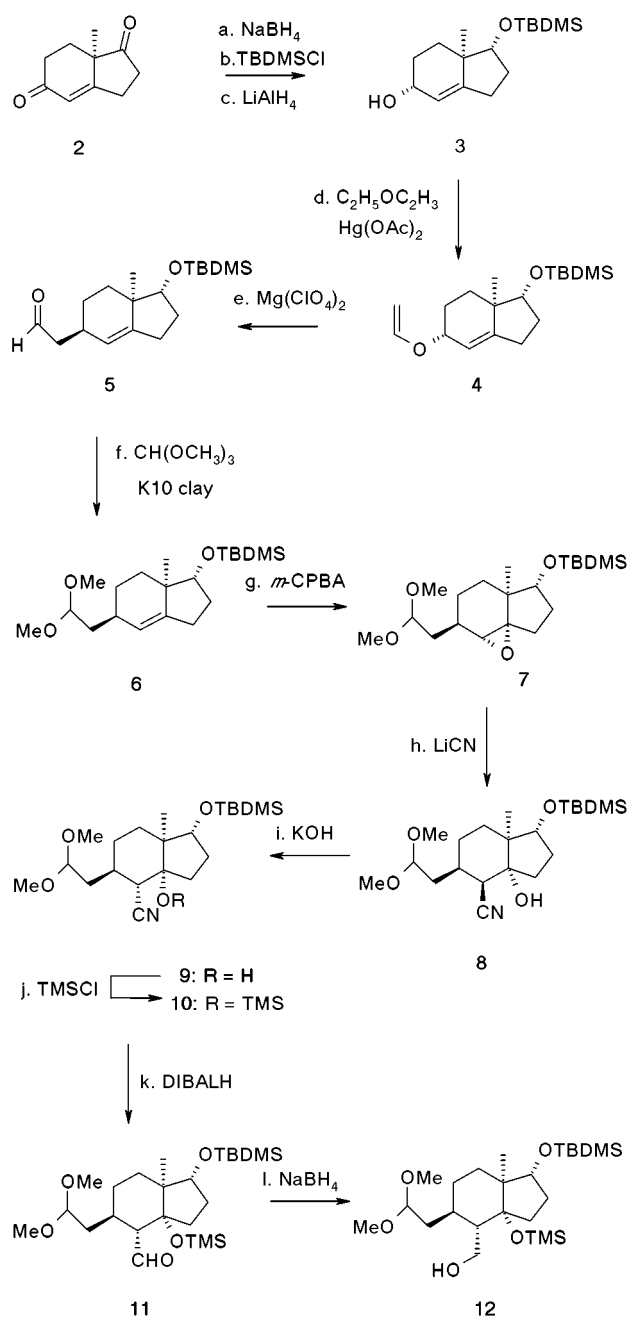
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Scheme 2. Synthesis of Alcohol 12^a

^a Reagents: (a) NaBH₄, EtOH, -10–5 °C (94%); (b) TBDMSCl, imidazole, DMAP, CH₂Cl₂ (82%); (c) LiAlH₄, Et₂O, -78 °C (90%); (d) C₂H₅OC₂H₃, Hg(OAc)₂, 40 °C (80%); (e) Mg(ClO₄)₂, CH₃NO₂ (83%); (f) CH(OCH₃)₃, montmorillonite clay K-10, Et₂O (98%); (g) *m*-CPBA, CH₂Cl₂, -5–0 °C (80%); (h) LiCN, THF, reflux (84%); (i) KOH, EtOH (69%); (j) TMSCl, imidazole, DMAP, CH₂Cl₂ (99%); (k) DIBALH, hexane (76%); (l) NaBH₄, EtOH, -10 °C (89%).

is readily available in enantiomerically pure form. Preliminary results have been disclosed previously as a short communication.⁸

Synthesis of Alcohol 12. The synthesis to the required alcohol **12** is shown in Scheme 2. The Hajos–Parrish diketone **2** was prepared in three steps using the described procedure⁹ except for the substitution of (*S*)-(-)-proline by (*R*)-(+)-proline. The proline-catalyzed in-

tramolecular aldol reaction afforded enantiomerically pure diketone **2** in 61% yield over all three steps. Optical purity was determined to be >95% by comparison of the optical rotation. The single asymmetric center was employed to control the remaining stereocenters. Chemoselective reduction of the isolated carbonyl function, which was then protected as TBDMS ether followed by reduction of the conjugated carbonyl function with LiAlH₄ gave allyl alcohol **3** in 69% yield.¹⁰ Vinyl transesterification of **3** with ethyl vinyl ether catalyzed by mercuric acetate resulted in the allyl vinyl ether **4** in 80% yield. Due to the hydrolytic instability of vinyl ethers,¹¹ the crude product was directly used for further transformations. Indeed, attempts to purify **4** by column chromatography gave only poor yields, and starting material **3** was isolated as the main product.

After treatment of **4** with catalytic amounts of LiClO₄¹² in nitromethane, the allylic ether underwent a [1,3] sigmatropic rearrangement; however, aldehyde **5** was only isolated in poor yield in this reaction. The yield of **5** could be greatly improved to 83% by replacement of LiClO₄ by Mg(ClO₄)₂. Aldehyde **5** showed to be thermally unstable which made careful evaporation of the solvent necessary. The only side product in this reaction was the diene, arising from elimination of the vinyl ether function in **4**, and could be isolated in 6% yield. No diastereoisomer at the C(5)-position was detected. After protection of the aldehyde function as the dimethylacetal with montmorillonite clay K-10¹³ as catalyst (→ **6**), the double bond was epoxidized with *m*-CPBA yielding epoxide **7** in 80% yield and in good stereoselectivity (α : β ~ 11:1). The mixture of both isomers was employed for the next step. Regiospecific ring opening of epoxide **7** with LiCN¹⁴ afforded stereoselectively β -hydroxy nitrile **8** in 84% yield. The β -isomer of **7** proved to be unreactive under these conditions. The yield of the reaction could be drastically improved by in situ preparation¹⁵ of LiCN (highly hygroscopic). Confirmation of the expected stereochemical outcome of the epoxidation and the ring opening reaction was obtained from X-ray crystallographic analysis of nitrile **8** (see Figure 2) which corroborated the relative configuration of the five stereocenters.¹⁶ As expected, the nitrile and the hydroxy group are in a trans-diaxial arrangement. The hydroxy group and the future tosylate substituent are in the desired antiperiplanar orientation which is necessary for the Grob-fragmentation reaction.

Nitrile **8** was then epimerized with ethanolic KOH to the thermodynamically more stable nitrile **9**. The configuration of that center was proved by ¹H NMR spectroscopy. The signal of H–C(4) was shifted toward higher field and a trans-diaxial coupling constant for H–C(4) of *J* = 12.1 Hz was observed. Since no reaction of **9** with

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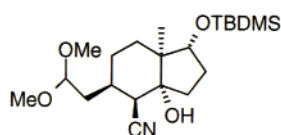
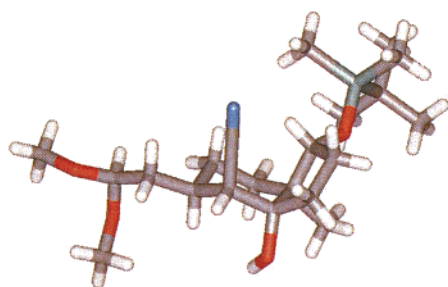
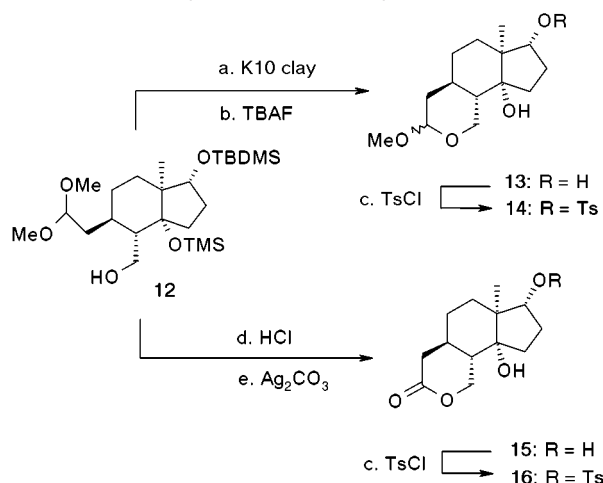
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(16) Crystallographic data (excluding structure factors) for the structures **8**, **17a**, **18** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC 147327, CCDC 147328, CCDC 147329. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ UK (fax: +44 (1223) 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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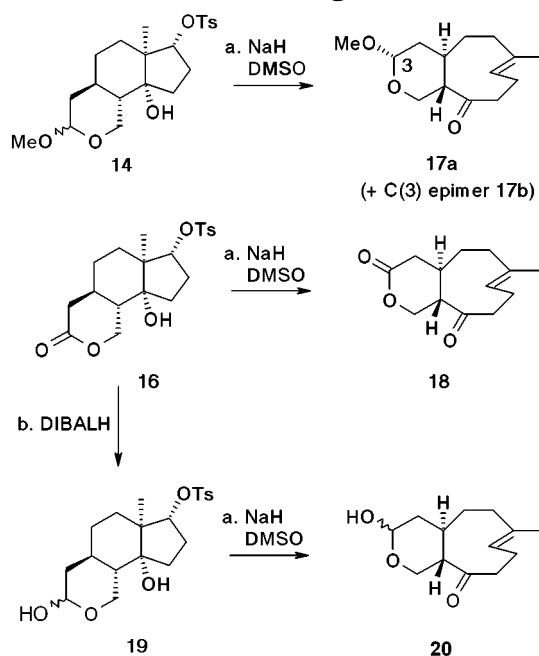
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**Figure 2.** X-ray crystal structure of β -hydroxy nitrile **8**.**Scheme 3. Syntheses of Tosylates **14** and **16**^a**

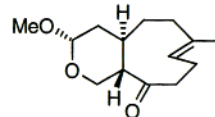
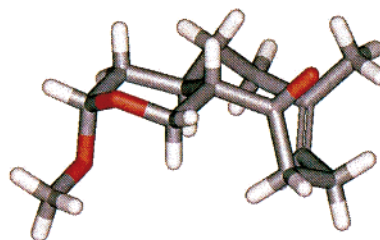
^a Reagents: (a) montmorillonite clay K-10, Et₂O (95%); (b) TBAF, THF (91%); (c) TsCl, pyridine, CHCl₃ (90% for **14**, 92% for **16**); (d) HCl, THF; (e) Ag₂CO₃ on Celite, benzene, reflux (61% for both steps).

DIBALH, even in large excess, to form an aldehyde occurred, it was assumed that the nonreactivity could be due to the neighboring free alcohol function. We therefore decided to protect the alcohol as the TMS ether (\rightarrow **10**) which was realized in almost quantitative yield. Reduction of **10** with DIBALH was now successful, and aldehyde **11** was isolated in 70% yield. Further reduction with NaBH₄ furnished alcohol **12** in 89% yield.

Syntheses of Tosylates **14 and **16**.** In the following part of the synthesis we investigated two different routes (shown in Scheme 3). In the first route, alcohol **12** was transacetalized by montmorillonite clay K-10 to give **13** (α : β 1.5:1) in 86% yield after standard removal of the TMS and TBDMS groups. Since the separation of the anomers was time consuming, it was decided to use the mixture for the tosylation which yielded **14** in 90%. In the second route, we were interested in tosylate **16**, in which the lactone function is already installed. Thus, alcohol **12** was treated with 2 N HCl in THF to give the desilylated hemiacetal in one step together with 32% of **13**. After careful neutralization and drying of the crude product, oxidation to the lactone **15** was performed by

Scheme 4. Grob-Fragmentation^a

^a Reagents: (a) NaH, DMSO (89% for **17a/b**, 71% for **18**, 88% for **20**); (b) DIBALH, CH₂Cl₂, -65 °C (98%).

**Figure 3.** X-ray crystal structure of cyclononenone **17a**.

refluxing for 6 h with Ag₂CO₃ on Celite¹⁷ in 61% yield. The methylacetal **13** could be recycled. Tosylation of **15** then afforded **16** in 92% yield.

Grob-Fragmentation. Scheme 4 summarizes the results on the fragmentation reaction. Compounds **14**, **16**, and **19** were treated at room temperature with the methylsulfinyl carbanion which was prepared in the usual way.¹⁸ The reaction was normally over within a few minutes, and the cyclononenones were isolated in good to excellent yields. So, the acetals **17a/17b** could be isolated in 89% yield in an epimeric ratio α : β \sim 2.2:1. Separation of the anomers was possible by column chromatography. Crystals of **17a** were obtained from hexane, and its structure was solved by X-ray crystallographic analysis (Figure 3).¹⁶ The crystal structure clearly shows the *E*-configuration of the endocyclic double bond. The six-membered ring is trans-fused and appears in a chair conformation. Our attention was also focused

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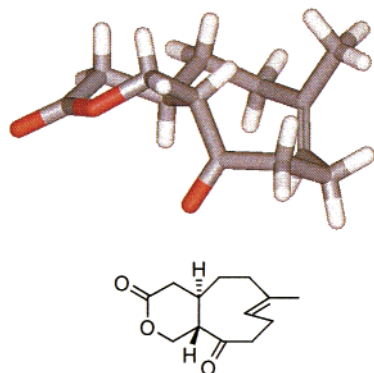
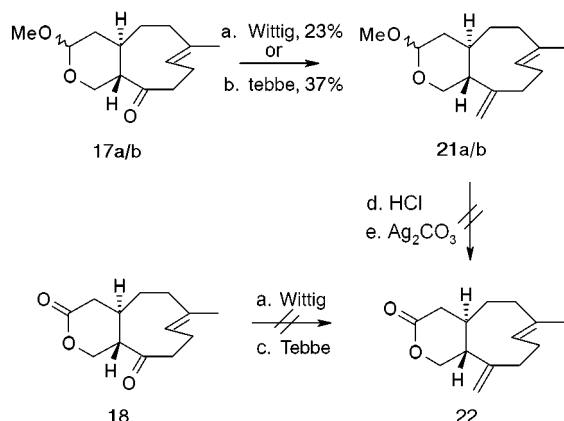


Figure 4. X-ray crystal structure of cyclononenone **18**.

Scheme 5. Conversion of the Cyclononenones^a



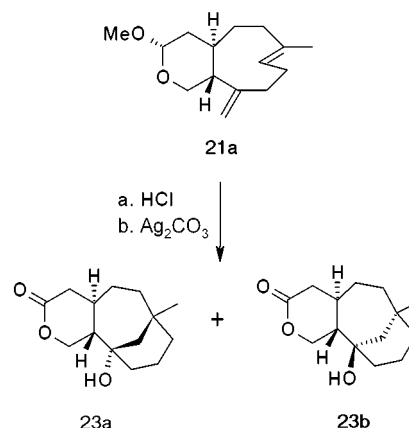
^a Reagents: (a) MePPh_3Br , $n\text{-BuLi}$, THF; (b) $\text{TiCp}_2\text{CH}_2\text{ClAlMe}_3$, THF; (c) Zn , CH_2Br_2 , THF, TiCl_4 ; (d) HCl , THF; (e) Ag_2CO_3 on Celite, benzene, reflux.

on the carbonyl group which appears in an almost parallel orientation with respect to the methyl group.

Likewise, fragmentation of **16** furnished cyclononenone **18** in 71% yield. To prevent further decomposition the reaction had to be quenched after 30 min by the addition of phosphate buffer (pH 7.0). X-ray crystallographic analysis (Figure 4) also confirmed the structure of **18**.¹⁶ In contrast to **17a** the six-membered ring appears now in a boat conformation allowing the preferred planar conformation of the ester function. Furthermore, both rings are again trans-fused and the endocyclic double bond had the desired *E*-configuration as expected. Compared to structure **17a** the carbonyl group is now in a different steric environment as a result of the different six-membered ring conformation. The Grob-fragmentation was also realized with lactol **19**, which was obtained by reduction of lactone **16** with DIBALH in 98% yield. Cyclononenone **20** was isolated in 88% yield as a mixture of both isomers ($\alpha:\beta \sim 56:44$). In none of the fragmentation reactions of **14**, **16**, and **19**, products with *Z*-configuration at the newly formed double bond could be isolated.

Conversion of the Cyclononenones. The introduction of the exocyclic double bond was planned by a classical Wittig-olefination of **17a** with methylene triphenylphosphorane and proved to be difficult (Scheme 5). Transformation of **17** afforded diene **21** in only 23% yield at the best, besides 20% of recovered starting material. Systematic variation of the reaction conditions did not raise the yield. Alternatively, methylenation with

Scheme 6. Acid-Catalyzed Cyclization of 21a^a



^a Reagents: (a) 0.5 M HCl , THF, 60 °C; (b) Ag_2CO_3 on Celite, benzene, reflux (61% for both steps).

the Tebbe-reagent¹⁹ was considered. Again, **21** was isolated in only 37% yield. Both **17a** and **17b** were employed separately in the olefination reaction and showed no difference in reactivity. Despite the poor yields, dienes **21a/b** were tried to be converted to lactone **22**. However, hydrolysis of the acetal function under acidic conditions followed by oxidation with Ag_2CO_3 on Celite did not result in the desired diene **22**. Mass spectra and extensive two-dimensional NMR experiments (HMBC and ROESY) showed a 1:1 mixture of two compounds that could be assigned as the structures **23a** and **23b** (Scheme 6). To explain the formation of **23**, an initial protonation of the endocyclic double bond followed by transannular ring closure seems plausible. Variations of the acids (H_2SO_4 , HCl , AcOH) and the concentrations did not affect the reaction, and **23a/b** were always isolated as the main products (ca. 60%). Compounds **23a/b** have not been reported in the literature and were not described as metabolites of the xenicanes so far. Similar carbocation induced transannular cyclizations, however, are well-known in the series of the caryophyllenes.²⁰ Attempts to convert the carbonyl group into the exocyclic double bond in **18** were completely unsuccessful (Scheme 5). Neither the Wittig-process nor the Tebbe-reaction (Lombardo-variant)²¹ showed any signs of product, and only starting material was recovered. Investigations with the "instant-ylide" variant²² were also unsuccessful. Since enolization of the ketone could be excluded by D_2O quenching experiments, we believe that the unreactivity is due to the different sterical environment of the carbonyl function in **18** compared to **17a/b**. Since the direct conversion could not be realized, we planned an epoxidation/deoxygenation pathway to form the olefin **22** (Scheme 7). Reaction of **18** with a large excess of dimethylsulfoxonium methylide^{23,24} at 65 °C (to effect any reaction) led to a product that was best characterized by two-dimensional NMR-spectroscopy as the epoxide **25**. Most probably, the strong basic conditions provoked an opening of the lactone ring via β -elimination to form the α,β -unsaturated ketone **24** as an intermediate.

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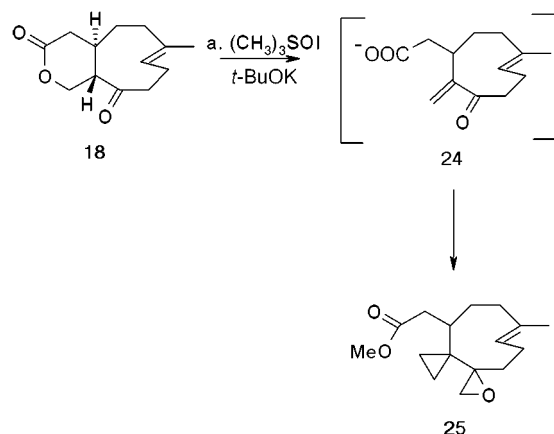
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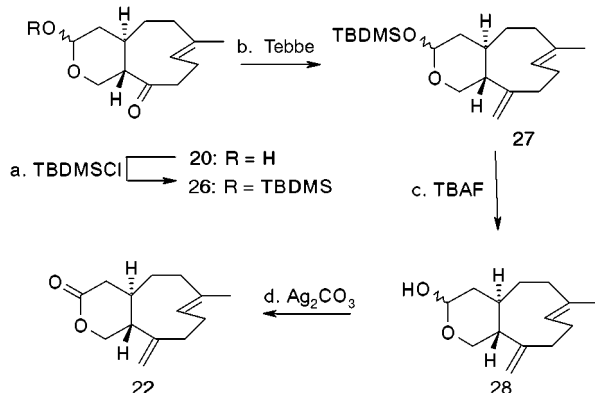
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Scheme 7. Epoxidation/Deoxygenation Pathway^a

^a Reagents: (a) $(\text{CH}_3)_3\text{SOI}$, $t\text{-BuOK}$, DMSO, 65 °C.

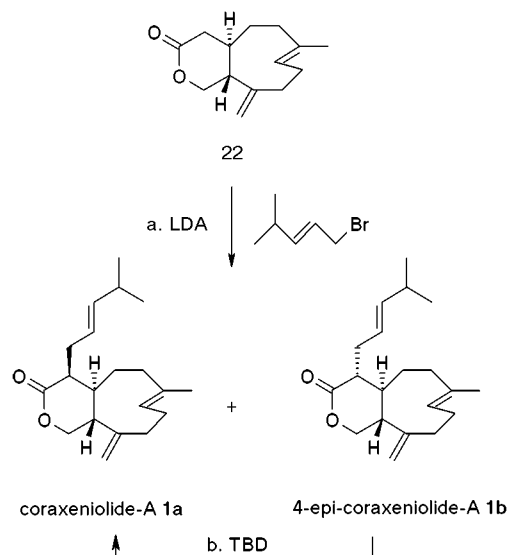
Scheme 8. Synthesis of Diene 22^a

^a Reagents: (a) TBDMSO, imidazole, CH_2Cl_2 (98%); (b) $\text{TiCp}_2\text{-CH}_2\text{ClAlMe}_3$, THF, pyridine, -5 °C–rt (70%); (c) TBAF, THF (85%); (d) Ag_2CO_3 on Celite, benzene, 60 °C (89%).

As a consequence of the experiments with the olefination of **17** and **18**, we decided to investigate the silylactal **26**. In **26** both, the elimination reaction as well as the problems with acetal hydrolysis should be suppressed.

Synthesis of Diene 22. Silylactal **26** was obtained by silylation of lactol **20** with TBDMSO in 98% yield as a mixture of epimers ($\alpha:\beta \sim 13:87$) (Scheme 8). Unexpectedly, no reaction of **26** occurred by treatment with methylene triphenylphosphorane. But diene **27** could be isolated in 70% yield by reaction with the Tebbe-reagent. A key requirement for the success of this reaction in good yield was the addition of pyridine. Acting as a Lewis-base, it is believed that it complexes with the aluminum to generate the reactive methylidene titanium. Deprotection of **27** with TBAF (85%) followed by oxidation with Ag_2CO_3 on Celite finally afforded diene **22** in 89% yield.

Introduction of the Side Chain. Deprotonation of **22** at -78 °C with LDA followed by treatment with 1-bromo-4-methylpent-2-ene (4:1 mixture with 3-bromo-4-methylpent-1-ene, prepared according to literature^{25,26,27}) led to the mixture of coraxeniolide-A and its C-(4) epimer in a ratio of **1a:1b** 1:5.7, from which coraxeniolide-A (**1a**) could be separated by column chromatography (Scheme 9). The alkylation was successfully realized even on the

Scheme 9. Alkylation and Epimerization^a

^a Reagents: (a) LDA, 1-bromo-4-methylpent-2-ene, THF, DMPU, -78 °C to -69 °C (50%); (b) TBD, toluene (80%).

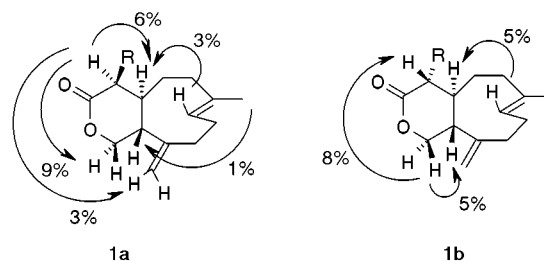


Figure 5. NOEs of **1a** and **1b**.

μmol -scale and afforded both isomers in 50% yield. The full set of spectroscopic data (IR, MS, ^{13}C and ^1H NMR, NOE) was in complete agreement with the data of coraxeniolide-A from natural sources.⁵ In addition, a crystal structure of **1a** confirmed the assignments and was within the limits identical to the one described. The structure of 4-*epi*-coraxeniolide-A (**1b**) was also verified by ^1H NMR NOE experiments (Figure 5). 4-*epi*-Coraxeniolide-A (**1b**) could be equilibrated with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) leading to a **1a:1b** 3:1 ratio.

Relative Stabilities of 1a and 1b. Accompanying the experimental epimerization reaction we investigated in the thermodynamically preferred configuration at C-4 by molecular modeling (see Experimental Section). Simulated annealing at 1000 K followed by full matrix minimization with the CFF91 force field²⁸ with the program Insight II showed that the natural coraxeniolide-A (**1a**) is about 0.6 kcal/mol more stable than the unnatural 4-*epi*-coraxeniolide-A (**1b**) (Figure 6). This corresponds extremely well with the experimental results.

As known from the literature,²⁹ xeniolides undergo slow conformation ring flipping of the nine-membered ring and appear as two separate conformers in solution on the NMR time scale. By NOE experiments, the prevailing conformer of coraxeniolide-A and some of its

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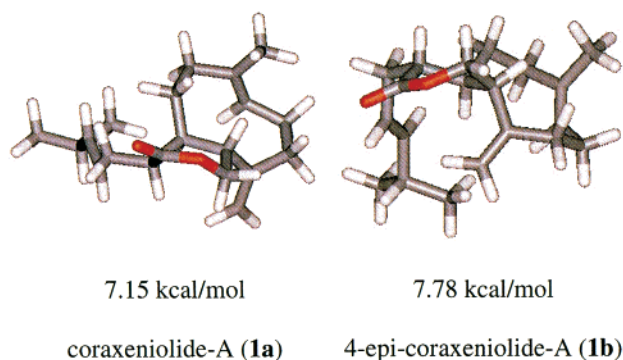
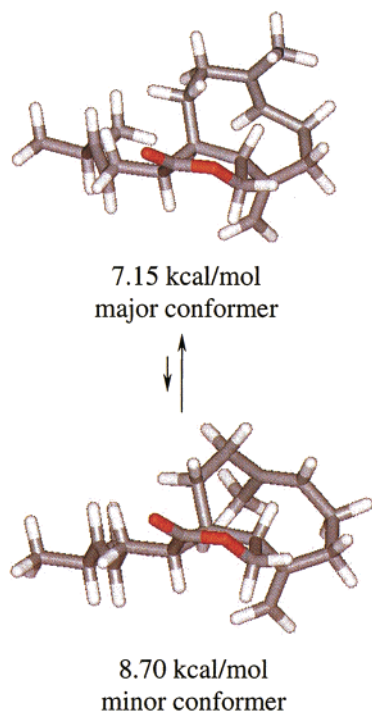


Figure 6. Lowest energy conformers for **1a** and **1b**.

Scheme 10. Lowest Energy Representatives of the Two Conformational Families with Inverted Nine-Membered Ring Conformation of 1a



intermediates was assigned to have Me(7) trans to H-C(4a), which is in agreement with published data on members of the xeniolide family. Equilibrium ratios varied from 1.8:1 in the case of **20** (β -isomer), where the six-membered ring is in a chair conformation, to 19:1 in the case of coraxeniolide-A (**1a**) where the six-membered ring is in a boat conformation. Molecular modeling for both conformers of **1a** confirmed our experimental observations and showed that the major conformer is by about 1.6 kcal/mol more stable (Scheme 10).

Conclusion. In conclusion, a highly stereocontrolled total synthesis of optically active coraxeniolide-A (**1a**) has been achieved. The synthesis relies on a Grob-fragmentation as key step for the stereospecific construction of the nine-membered ring. Given the late introduction of the side chain in the lactone ring, this method may prove useful in the preparation of a wide variety of members of the xeniolide family.

Experimental Section

General. All experiments were carried out under Ar. Solvents were distilled prior to use. All moisture sensitive reactions were performed in oven-dried glassware. External

bath temperatures were used to record all reaction temperatures. Spectral data (NMR, IR, MS, optical rotation, melting points) were measured with standard equipment and are indicated in standard format.

Molecular Modeling Calculations. All calculations were performed using the CFF91 force field²⁸ as implemented in the Insight II v.98/Discover v.2.9.8 program package from Molecular Simulations, Inc. on an Octane workstation from SGI. The natural coraxeniolide-A (**1a**) was built in the conformation, determined by NOE experiments which is similar to the one obtained from X-ray structure determination.⁵ This structure was fully minimized using the Steepest Descent algorithm (down to a gradient of 10 kcal·mol⁻¹·Å⁻¹) followed by the Newton–Raphson algorithm (down to a gradient of 0.001 kcal·mol⁻¹·Å⁻¹). The 4-*epi*-coraxeniolide-A (**1b**) was constructed starting from the minimized conformation of **1a**, inverting the configuration of the α -carbon and constraining the lactone ring in the boat conformation with the side chain in equatorial position. The structure was then fully minimized as described for **1a**. Both structures were then submitted to a simulated annealing procedure in order to scan the conformational space. The energy calculations of the two ring-flipped conformers of **1a** were performed in analogy.

Compounds **2** and **3** were prepared according to the procedures reported previously, but in enantiomerically pure form.^{9,10} Yields and optical rotation data are given below.

(7aR)-7a-Methyl-2,3,7,7a-tetrahydro-6H-indene-1,5-dione (2). It was prepared in three steps in 61% yield. $[\alpha]_{\text{D}}^{24}$ –359 (*c* 4.8, benzene).⁹

(1R,5aR,7aR)-1-(tert-Butyldimethylsilanyloxy)-7a-methyl-2,3,7,7a-tetrahydro-1H,6H-inden-5-one (3). It was prepared in three steps starting from **2** in 69% yield. $[\alpha]_{\text{D}}^{25}$ –28 (*c* 4.7, CHCl₃).^{10b}

(1R,5R,7aR)-tert-Butyldimethyl-(7a-methyl-5-vinyloxy-2,3,5,6,7,7a-hexahydro-1H-inden-1-yloxy)silane (4). To a solution of alcohol **3** (1.55 g, 5.49 mmol) in 40 mL of ethyl vinyl ether were added Hg(OAc)₂ (1.84 g, 5.76 mmol) and NaOAc·3H₂O (52 mg, 0.39 mmol). The reaction mixture was heated at 40 °C for 20 h. The solution was cooled (10 °C), and 15 mL Et₂O was added, followed by 5 mL of 15% NaOH solution during which time a white precipitate developed. Then 0.87 mL of a 12% NaBH₄ solution in 14 M NaOH was added. The mixture was allowed to stir for 1.5 h during which time the mercury metal precipitates. The suspension was decanted and the aqueous layer extracted with Et₂O. The combined organic layers were washed with brine, dried (Na₂SO₄), and filtered through a pad of Celite. Evaporation of the solvent afforded 1.36 g (80%) of allyl vinyl ether **4** as a yellow oil which was of sufficient purity for the next step. Data for **4**: *R*_f 0.54 (3% EtOAc/hexane); $[\alpha]_{\text{D}}^{25}$ +31.8 (*c* 4.96, CHCl₃); IR 1632 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.03 (s, 6H), 0.89 (s, 9H), 1.00 (s, 3H), 1.27–1.39 (m, 1H), 1.64–1.88 (m, 4H), 2.00–2.13 (m, 2H), 2.42–2.48 (m, 1H), 3.55 (dd, *J* = 8.1, 9.6 Hz, 1H), 4.01 (dd, *J* = 1.5, 6.6 Hz, 1H), 4.32 (dd, *J* = 1.5, 14.3 Hz, 1H), 4.42 (m, 1H), 5.40 (s, 1H), 6.38 (dd, *J* = 6.6, 14.3 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ –4.91, –4.52, 16.50, 17.94, 25.71, 25.76, 29.56, 33.90, 34.04, 44.08, 68.54, 75.88, 81.22, 88.31, 118.86, 150.24; MS (EI) *m/z* 265 (100).

(1R,5R,7aR)-[1-tert-Butyldimethylsilanyloxy]-7a-methyl-2,3,5,6,7,7a-hexahydro-1H-inden-5-yl]acetaldehyde (5). To a solution of allyl vinyl ether **4** (2.52 g, 8.16 mmol) in 50 mL freshly distilled CH₃NO₂ was added Mg(ClO₄)₂ aq (91 mg, 0.41 mmol). The mixture became cloudy after a few minutes and was stirred for 3 h. Concentration and purification by flash chromatography (SiO₂, 3% EtOAc/hexane) provided 2.09 g (83%) of aldehyde **5** as a colorless oil. Data for **5**: *R*_f 0.41 (3% EtOAc/hexane); $[\alpha]_{\text{D}}^{25}$ –109.3 (*c* 5.0, CHCl₃); IR 1720 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.00 (s, 6H), 0.86 (s, 9H), 0.88 (s, 3H), 1.06 (td, *J* = 2.9, 13.2 Hz, 1H), 1.23 (m, 1H), 1.39 (m, 1H), 1.53–1.62 (m, 2H), 1.77–1.89 (m, 2H), 1.98–2.11 (m, 1H), 2.32–2.38 (m, 2H), 2.66 (m, 1H), 3.50 (dd, *J* = 8.1, 9.2 Hz, 1H), 5.20 (d, *J* = 1.1 Hz, 1H), 9.72 (brt, *J* = 2.2 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ –4.81, –4.43, 16.72, 18.01, 23.97, 25.79, 28.71, 29.74, 30.74, 43.59, 49.98, 81.74, 121.39, 146.56, 202.57; MS (EI) *m/z* 251 (100).

(1*R*,5*R*,7*aR*)-tert-Butyl-[5-(2,2-dimethoxyethyl)-7*a*-methyl-2,3,5,6,7,7*a*-hexahydro-1*H*-inden-1-yloxy]dimethylsilane (6). A suspension of montmorillonite clay K-10 (15 g) and CH(OCH₃)₃ (22 mL) was stirred for 30 min. A solution of aldehyde **5** (7.37 g, 23.88 mmol) in 66 mL of Et₂O was added, and stirring was continued for further 3.5 h. The mixture was filtered through a pad of Celite and washed with Et₂O. The organic layer was washed with saturated aqueous NaHCO₃ solution and brine, dried (Na₂SO₄) and evaporated to give 8.37 g (98%) of methylacetal **6** as a yellow oil. Data for **6**: *R*_f 0.69 (10% EtOAc/toluene); [α]_D²⁵ −90.4 (c 2.6, CHCl₃); IR 1472, 2966 cm^{−1}; ¹H NMR (300 MHz, CDCl₃) δ 0.02, 0.03 (2s, 6H), 0.89 (s, 3H), 0.90 (s, 9H), 1.13 (td, *J* = 2.9, 13.6 Hz, 1H), 1.44–1.64 (m, 5H), 1.73–1.91 (m, 2H), 2.00–2.10 (m, 1H), 2.19 (m, 1H), 2.44 (m, 1H), 3.32 (s, 3H), 3.32 (s, 3H), 3.53 (dd, *J* = 8.1, 9.2 Hz, 1H), 4.47 (dd, *J* = 5.5, 5.9 Hz, 1H), 5.28 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ −4.09, −3.74, 17.51, 18.75, 24.76, 26.51, 26.77, 30.58, 30.72, 31.66, 39.18, 44.49, 53.13, 53.20, 82.51, 103.94, 123.59, 145.67; MS (EI) *m/z* 322 (46), 265 (100).

(1*R*,2*R*,4*aS*,5*R*,7*aR*)-tert-Butyl-[2-(2,2-dimethoxyethyl)-4*a*-methyloctahydro-1-oxacyclopropa[*d*]inden-5-yloxy]dimethylsilane (7). A solution of methylacetal **6** (6.75 g, 19.03 mmol) in 100 mL of CH₂Cl₂ was cooled to −5 °C, and a solution of *m*-CPBA (6.57 g, 26.64 mmol) in 200 mL of CH₂Cl₂ was added over a period of 40 min. After stirring for 4 h at −5 °C, the mixture was washed with saturated Na₂SO₃ solution, saturated aqueous NaHCO₃ solution, dried (Na₂SO₄), and evaporated. Purification by flash chromatography (SiO₂, 20% EtOAc/hexane + 0.5% Et₃N) yielded 5.64 g (80%) of epoxide **7** and 0.49 g (7%) of the β-isomer both as a colorless oil. Data for **7**: *R*_f 0.48 (20% EtOAc/hexane); (β-isomer): [α]_D²⁵ −70.5 (c 0.70, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 0.03 (s, 6H), 0.88 (s, 9H), 0.92 (s, 3H), 1.09–1.14 (m, 1H), 1.16–1.22 (m, 2H), 1.47–1.59 (m, 1H), 1.61–1.66 (m, 1H), 1.67–1.80 (m, 4H), 1.85–1.92 (m, 1H), 2.05 (m, 1H), 2.88 (d, *J* = 1.1 Hz, 1H), 3.34 (s, 6H), 3.79 (m, 1H), 4.49 (t, *J* = 5.9 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ −4.90, −4.38, 15.23, 17.01, 21.50, 25.72, 27.43, 29.54, 29.86, 30.80, 34.55, 40.76, 52.80, 52.94, 64.29, 66.25, 79.79, 103.42.

(1*R*,3*aR*,4*S*,5*R*,7*aS*)-1-(tert-Butyldimethylsilyloxy)-5-(2,2-dimethoxyethyl)-3*a*-hydroxy-7*a*-methyloctahydroindene-4-carbonitrile (8). A cooled (0 °C), vigorous stirred suspension of LiH (550 mg, 69.33 mmol) in 170 mL of THF was treated carefully with (CH₃)₂C(OH)CN (5.3 mL, 57.79 mmol). The ice bath was removed and the mixture stirred for 5 h at room temperature. Epoxide **7** (4.20 g, 13.0 mmol) in a mixture with the β-isomer, dissolved in 25 mL of THF, was then slowly added and the solution heated to reflux for 19 h. H₂O was added, THF evaporated, and the resulting oily solution extracted with Et₂O. The organic layer was washed with saturated aqueous NaHCO₃ solution and brine, dried (Na₂SO₄), and evaporated. Purification by flash chromatography (SiO₂, 3:1 hexane/EtOAc) yielded 3.77 g (84%) of nitrile **8** as a white solid. Crystals of **8** suitable for X-ray structure determination were obtained from hexane. Data for **8**: mp 92–93 °C; *R*_f 0.21 (3:1 hexane/EtOAc); [α]_D²⁷ −21.5 (c 1.97, CHCl₃); IR 2240, 3487 cm^{−1}; ¹H NMR (300 MHz, CDCl₃) δ 0.05 (s, 6H), 0.88 (s, 9H), 0.95 (s, 3H), 1.15–1.30 (m, 1H), 1.42–1.48 (m, 1H), 1.50–1.58 (m, 3H), 1.61–1.78 (m, 2H), 2.01–2.11 (m, 4H), 2.67 (br, D₂O exchange, 1H), 2.91 (d, *J* = 5.1 Hz, 1H), 3.32 (s, 3H), 3.33 (s, 3H), 4.19 (brt, *J* = 6.3 Hz, 1H), 4.42 (dd, *J* = 4.8, 6.3 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ −5.07, −4.57, 16.02, 17.87, 23.76, 25.74, 28.86, 29.96, 31.10, 34.90, 36.06, 41.96, 48.09, 52.45, 53.29, 76.71, 80.16, 103.04, 119.81; MS (LSIMS) *m/z* 396 (11), 366 (100). Anal. Calcd for C₂₁H₃₀SiO₄N: C, 63.43; H, 9.89; N, 3.52. Found: C, 63.30; H, 9.71; N, 3.55.

(1*R*,3*aR*,4*S*,5*R*,7*aS*)-1-(tert-Butyldimethylsilyloxy)-5-(2,2-dimethoxyethyl)-3*a*-hydroxy-7*a*-methyloctahydroindene-4-carbonitrile (9). To a solution of nitrile **8** (5.87 g, 14.76 mmol) in 70 mL of EtOH was added 58 mL of 2 N aqueous KOH solution. The mixture was stirred overnight at room temperature and then heated to 50 °C for 2 h. H₂O was added and the aqueous layer extracted with Et₂O. The organic layer was dried (Na₂SO₄) and evaporated. Purification by flash chromatography (SiO₂, 3:1 to 1:1 hexane/EtOAc) yielded 4.05

g (69%) of nitrile **9** as a white solid and 1.30 g (22%) of nitrile **8**. Data for **9**: mp 103 °C; *R*_f 0.35 (3:1 hexane/EtOAc); [α]_D²⁷ −24.8 (c 2.94, CHCl₃); IR 2240, 3471 cm^{−1}; ¹H NMR (300 MHz, CDCl₃) δ 0.02 (s, 6H), 0.88 (s, 9H), 0.93 (s, 3H), 1.13 (ddd, *J* = 4.0, 13.6, 17.7 Hz, 1H), 1.34 (td, *J* = 4.4, 14.0 Hz, 1H), 1.43–1.49 (m, 1H), 1.55 (m, 1H), 1.62–1.71 (m, 1H), 1.72–1.81 (m, 2H), 1.90–2.03 (m, 3H), 2.05–2.12 (m, 1H), 2.21 (br, D₂O exchange, 1H), 2.33 (d, *J* = 12.1 Hz, 1H), 3.31 (s, 3H), 3.35 (s, 3H), 4.02 (brt, *J* = 7.7 Hz, 1H), 4.55 (dd, *J* = 4.8, 6.6 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ −4.99, −4.42, 16.77, 17.87, 25.67, 26.18, 28.52, 28.65, 31.94, 35.43, 37.04, 45.17, 46.62, 51.43, 53.37, 71.78, 78.10, 102.00, 120.03; MS (LSIMS) *m/z* 367 (25), 366 (100). Anal. Calcd for C₂₁H₃₀SiO₄N: C, 63.43; H, 9.89; N, 3.52. Found: C, 63.36; H, 9.83; N, 3.52.

(1*R*,3*aR*,4*S*,5*R*,7*aS*)-1-(tert-Butyldimethylsilyloxy)-5-(2,2-dimethoxyethyl)-7*a*-methyl-3*a*-trimethylsilyloxyoctahydroindene-4-carbonitrile (10). To a solution of nitrile **9** (5.0 g, 12.57 mmol) in 100 mL of CH₂Cl₂ was added in portions imidazole (2.57 g, 37.72 mmol). TMSCl (4.0 mL, 31.43 mmol) was added dropwise followed by DMAP (500 mg). After stirring for 24 h, H₂O was added and the aqueous layer extracted with EtOAc. The combined organic layers were dried (MgSO₄) and evaporated. Purification by flash chromatography (SiO₂, 3:1 hexane/EtOAc) yielded 5.8 g (99%) of **10** as a viscous colorless oil. Data for **10**: *R*_f 0.68 (3:1 hexane/EtOAc); [α]_D²⁷ −13.3 (c 0.62, CHCl₃); IR 2240 cm^{−1}; ¹H NMR (300 MHz, CDCl₃) δ 0.00, 0.01 (2s, 6H), 0.22 (s, 9H), 0.83 (s, 3H), 0.88 (s, 9H), 1.10 (ddd, *J* = 4.4, 13.6, 18.0 Hz, 1H), 1.27–1.32 (m, 1H), 1.35–1.50 (m, 2H), 1.57–1.68 (m, 2H), 1.68–1.73 (m, 1H), 1.88–2.01 (m, 2H), 2.03–2.14 (m, 2H), 2.24 (d, *J* = 11.8 Hz, 1H), 3.30 (s, 3H), 3.35 (s, 3H), 3.98 (brt, *J* = 7.0 Hz, 1H), 4.56 (dd, *J* = 4.8, 7.0 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ −4.99, −4.43, 2.57, 17.86, 18.16, 25.67, 26.59, 28.49, 28.93, 31.54, 34.30, 36.83, 45.74, 47.63, 50.65, 53.61, 70.82, 82.07, 101.80, 120.66; MS (LSIMS) *m/z* 468 (9), 438 (100).

(1*R*,3*aR*,4*S*,5*R*,7*aS*)-1-(tert-Butyldimethylsilyloxy)-5-(2,2-dimethoxyethyl)-7*a*-methyl-3*a*-trimethylsilyloxyoctahydroindene-4-carbaldehyde (11). To a chilled (−60 °C) solution of silyl ether **10** (3.0 g, 6.38 mmol) in 75 mL of hexane was added dropwise DIBALH (19.2 mL, 1 M in hexane, 19.2 mmol). The mixture was allowed to warm to room temperature and was stirred for further 4 h. While cooling (0 °C), MeOH was added followed by H₂O, and stirring was continued for 1 h. The aqueous layer was separated and extracted with Et₂O, and the combined organic layers were washed with brine, dried (MgSO₄), and evaporated. Purification by flash chromatography (SiO₂, 5:1 hexane/EtOAc) afforded 2.3 g (76%) of aldehyde **11** as a colorless oil. Data for **11**: *R*_f 0.48 (5:1 hexane/EtOAc); [α]_D²⁷ +37.5 (c 1.20, CHCl₃); IR 1716 cm^{−1}; ¹H NMR (300 MHz, CDCl₃) δ 0.00 (s, 6H), 0.09 (s, 9H), 0.79 (s, 3H), 0.87 (s, 9H), 1.11 (ddd, *J* = 4.8, 12.9, 17.6 Hz, 1H), 1.21–1.52 (m, 5H), 1.52–1.63 (m, 2H), 1.66 (dd, *J* = 4.8, 11.8 Hz, 1H), 1.75 (dd, *J* = 3.3, 13.6 Hz, 1H), 1.83–2.02 (m, 4H), 2.18–2.32 (m, 1H), 3.29 (s, 3H), 4.01 (brdd, *J* = 7.4, 8.5 Hz, 1H), 4.49 (dd, *J* = 4.1, 7.4 Hz, 1H), 9.56 (d, *J* = 4.8 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ −4.93, −4.38, 2.51, 17.72, 17.84, 25.75, 26.06, 28.86, 28.90, 32.37, 37.15, 48.07, 51.98, 52.91, 60.94, 70.99, 83.17, 102.25, 208.17; MS (LSIMS) *m/z* 441 (63), 133 (100).

(1*R*,3*aR*,4*S*,5*R*,7*aS*)-[1-(tert-Butyldimethylsilyloxy)-5-(2,2-dimethoxyethyl)-7*a*-methyl-3*a*-trimethylsilyloxyoctahydroindene-4-yl]-methanol (12). A solution of aldehyde **11** (1.20 g, 2.53 mmol) in 16 mL of EtOH was cooled to −10 °C, and NaBH₄ (47 mg, 1.26 mmol) was added in portions. The mixture was stirred at this temperature and quenched after 1.5 h with 2 N HCl to adjust the pH to 5–7. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with saturated aqueous NaHCO₃ solution and brine, dried (MgSO₄), and evaporated. Purification by flash chromatography (SiO₂, 3:1 hexane/EtOAc) afforded 1.07 g (89%) of alcohol **12** as a colorless oil. Data for **12**: *R*_f 0.46 (3:1 hexane/EtOAc); [α]_D²⁷ −6.4 (c 1.60, CHCl₃); IR 3250 cm^{−1}; ¹H NMR (300 MHz, CDCl₃) δ 0.01 (s, 6H), 0.15 (s, 9H), 0.79 (s, 3H), 0.88 (s, 9H), 1.02 (dt, *J* = 2.9, 11.8 Hz, 1H), 1.20–1.29 (m, 2H), 1.42–1.48 (m, 2H), 1.60–1.64 (m, 2H), 1.72–1.82 (m,

1H), 1.83–1.91 (m, 1H), 1.92–1.99 (m, 2H), 2.00–2.09 (m, 1H), 2.31 (br, D₂O exchange, 1H), 3.31 (s, 3H), 3.35 (s, 3H), 3.72 (dd, $J = 2.9, 11.8$ Hz, 1H), 3.78 (dd, $J = 2.9, 11.8$ Hz, 1H), 4.11 (m, 1H), 4.57 (dd, $J = 5.1, 7.0$ Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ -4.88, -4.34, 2.93, 17.96, 18.73, 25.78, 26.74, 29.15, 29.40, 31.63, 32.81, 35.94, 48.09, 49.16, 51.19, 53.56, 62.49, 71.25, 85.58, 102.89; MS (LSIMS) m/z 411 (24), 133 (100).

(3*R,S*,4*aR*,6*aS*,7*R*,9*aR*,9*bS*)-3-Methoxy-6*a*-methyl-decahydrocyclopenta[*h*]isochromene-7,9*a*-diol (13). To a solution of **12** (1.13 g, 2.37 mmol) in 30 mL of Et₂O was added montmorillonite clay K-10 (2 g), and the resulting suspension was stirred for 2 h. It was filtered through a pad of Celite and washed with Et₂O. The organic layer was washed with brine, dried (Na₂SO₄), and evaporated. Drying under high vacuum afforded 1.05 g (95%) of the acetal as a slightly yellow oil. The crude product was dissolved in 18 mL of THF, and TBAF·3H₂O (1.4 g, 4.50 mmol) was added. After stirring for 24 h, more TBAF (8.96 mL, 1 M in THF, 8.96 mmol) was added and stirring continued for further 3 days. H₂O was added, the aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine. Drying (Na₂SO₄), evaporation of the solvent, and purification by flash chromatography (SiO₂, 1:5 hexane/EtOAc) afforded 0.50 g (91%) of methylacetal **13** in an anomer mixture of α : β 1.5:1 as a white solid. Data for α -isomer: mp 135–136 °C; R_f 0.31 (1:5 hexane/EtOAc); $[\alpha]_D^{24} +70.7$ (c 0.87, CHCl₃); IR 3620 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.86 (s, 3H), 1.15 (dd, $J = 4.4, 12.5$ Hz, 1H), 1.19–1.29 (m, 1H), 1.31–1.38 (m, 2H), 1.37–1.40 (m, 1H), 1.58–1.67 (m, 3H), 1.70–1.78 (m, 1H), 1.83–1.96 (m, 2H), 2.08–2.12 (m, 1H), 3.34 (s, 3H), 3.65 (dd, $J = 4.1, 11.0$ Hz, 1H), 3.78 (t, $J = 11.0$ Hz, 1H), 4.29 (brt, $J = 7.7$ Hz, 1H), 4.67 (d, $J = 3.3$ Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 16.24, 27.91, 28.50, 28.96, 29.33, 32.29, 37.46, 45.01, 47.34, 54.51, 59.35, 72.18, 78.12, 98.00. Data for β -isomer: R_f 0.27 (1:5 hexane/EtOAc); $[\alpha]_D^{24} -56.9$ (c 0.45, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 0.86 (s, 3H), 1.13–1.35 (m, 5H), 1.45–1.51 (m, 1H), 1.60–1.71 (m, 3H), 1.82 (ddd, $J = 2.2, 3.7, 12.8$ Hz, 1H), 1.94–1.99 (m, 1H), 2.02–2.10 (m, 1H), 3.46 (s, 3H), 3.52 (t, $J = 10.3$ Hz, 1H), 4.08 (dd, $J = 3.7, 11.8$ Hz, 1H), 4.30 (m, 2H).

(3*R,S*,4*aR*,6*aS*,7*R*,9*aR*,9*bS*)-Toluene-4-sulfonic Acid 9*a*-Hydroxy-3-methoxy-6*a*-methyldecahydrocyclopenta[*h*]isochromen-7-yl Ester (14). To a solution of methylacetal **13** (0.64 g, 2.49 mmol) in 4.5 mL of CHCl₃ and 0.39 mL of pyridine was added TsCl (0.97 g, 4.98 mmol). After stirring for 1.5 days, H₂O was added and the aqueous layer extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. Purification by flash chromatography (SiO₂, 1:5 hexane/EtOAc) yielded 0.90 g (90%) of tosylate **14** (epimeric mixture α : β 1.45:1) as a colorless oil. Data for α -isomer: R_f 0.59 (1:5 hexane/EtOAc); $[\alpha]_D^{22} +64.3$ (c 1.40, CHCl₃); IR 1360, 3620 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.83–0.94 (m, 1H), 0.91 (s, 3H), 1.10–1.16 (m, 1H), 1.24–1.32 (m, 4H), 1.42–1.47 (m, 1H), 1.68–1.90 (m, 5H), 2.46 (s, 3H), 3.32 (s, 3H), 3.59 (dd, $J = 3.7, 11.0$ Hz, 1H), 3.73 (t, $J = 11.0$ Hz, 1H), 4.65 (d, $J = 3.3$ Hz, 1H), 4.89 (brt, $J = 7.0$ Hz, 1H), 7.35 (d, $J = 8.1$ Hz, 2H), 7.79 (d, $J = 8.1$ Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 17.00, 21.62, 25.60, 27.59, 28.55, 29.07, 32.14, 37.27, 44.93, 54.51, 59.04, 81.50, 97.90, 127.80, 129.78. Data for β -isomer: R_f 0.55 (1:5 hexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 0.89–0.94 (m, 1H), 0.92 (s, 3H), 1.03–1.11 (m, 2H), 1.26–1.30 (m, 3H), 1.43–1.49 (m, 1H), 1.63–1.91 (m, 5H), 2.45 (s, 3H), 3.42 (t, $J = 11.0$ Hz, 1H), 3.46 (s, 3H), 4.02 (dd, $J = 3.7, 11.8$ Hz, 1H), 4.27 (dd, $J = 2.2, 9.6$ Hz, 1H), 4.77–4.82 (m, 2H), 7.36 (d, $J = 7.7$ Hz, 2H), 7.79 (d, $J = 8.5$ Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 16.73, 25.49, 28.66, 32.69, 33.26, 38.35, 44.80, 47.17, 56.03, 65.75, 81.25, 102.76, 127.87, 129.80.

(4*aR*,6*aS*,7*R*,9*aR*,9*bS*)-7,9*a*-Dihydroxy-6*a*-methyl-decahydrocyclopenta[*h*]isochromen-3-one (15). To a solution of alcohol **12** (1.03 g, 2.17 mmol) in 10 mL of THF was added 1.5 mL of 2 N aqueous HCl. After 3 days, further 2 N HCl (1 mL) was added and the mixture stirred for 1 more day. Saturated aqueous NaHCO₃ solution was then added to adjust the pH to 7, the THF was evaporated, and the mixture was lyophilized. The resulting white powder was then extracted

with EtOAc in a Soxhlet apparatus overnight. Evaporation of the solvent and drying overnight under high vacuum resulted a white foam. This was dissolved in 20 mL of benzene, and Ag₂CO₃ on Celite (2.7 g, 4.50 mmol) was added. The suspension was heated to reflux for 6 h during which time the color turned to black. It was filtered through a pad of Celite and washed with EtOAc. Evaporation of the solvent and purification by flash chromatography (SiO₂, EtOAc) yielded 320 mg (61%) of lactone **15** as a white solid and 177 mg (32%) of methylacetal **13** as a colorless oil. Crystals of **15** were obtained from EtOAc. Data for **15**: mp 165 °C; R_f 0.30 (EtOAc); $[\alpha]_D^{24} -51.9$ (c 0.98, CHCl₃); IR 1727, 3448, 3619 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.91 (s, 3H), 1.19–1.27 (m, 1H), 1.34–1.39 (m, 1H), 1.45 (td, $J = 4.4, 11.8$ Hz, 1H), 1.48–1.53 (m, 1H), 1.64–1.72 (m, 3H), 1.92–1.99 (m, 2H), 2.07–2.16 (m, 2H), 2.75 (dd, $J = 5.5, 18.0$ Hz, 1H), 4.29 (m, 1H), 4.38 (t, $J = 11.4$ Hz, 1H), 4.47 (dd, $J = 4.4, 11.8$ Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 16.66, 28.50, 29.03, 29.07, 31.98, 34.02, 37.56, 42.85, 47.91, 71.39, 72.24, 78.74, 171.47; MS (EI) m/z 220 (60), 54 (100). Anal. Calcd for C₁₃H₂₀O₄: C, 64.98; H, 8.39. Found: C, 64.99; H, 8.22.

(4*aR*,6*aS*,7*R*,9*aR*,9*bS*)-Toluene-4-sulfonic Acid 9*a*-Hydroxy-6*a*-methyl-3-oxodecahydrocyclopenta[*h*]isochromen-7-yl Ester (16). To a solution of lactone **15** (303 mg, 1.26 mmol) in 2 mL of CHCl₃ was added 0.21 mL of pyridine followed by TsCl (601 mg, 3.15 mmol). The resulting suspension was stirred for 22 h at room temperature when another portion of TsCl (120 mg, 0.63 mmol) was added. After 45 h, the reaction was quenched by the addition of H₂O. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried (MgSO₄), and evaporated. Purification by flash chromatography (SiO₂, EtOAc) resulted 460 mg (92%) of tosylate **16** as a white foam. Data for **16**: R_f 0.55 (EtOAc); $[\alpha]_D^{24} +0.2$ (c 0.90, CHCl₃); IR 1361, 1726, 3446, 3609 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.91 (m, 1H), 0.95 (s, 3H), 1.25–1.31 (m, 1H), 1.36 (td, $J = 4.1, 12.5$ Hz, 1H), 1.42–1.53 (m, 2H), 1.69–1.82 (m, 2H), 1.83–1.88 (m, 1H), 1.89–2.00 (m, 2H), 2.08 (dd, $J = 11.8, 18.0$ Hz, 1H), 2.46 (s, 3H), 2.72 (dd, $J = 5.9, 18.0$ Hz, 1H), 4.33 (dd, $J = 10.3, 11.4$ Hz, 1H), 4.41 (dd, $J = 4.4, 11.4$ Hz, 1H), 4.85–4.90 (m, 1H), 7.35 (d, $J = 7.7$ Hz, 2H), 7.79 (d, $J = 8.1$ Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 16.73, 21.63, 25.56, 27.50, 28.05, 31.14, 33.12, 36.69, 42.12, 47.12, 70.22, 80.50, 127.79, 129.87, 133.86, 144.97, 171.12; MS (LSIMS) m/z 395 (54), 136 (100); HR/LSIMS m/z calcd for C₂₀H₂₇O₆S 395.1528, found 395.1530.

(3*S*,4*aR*,11*aS*)-3-Methoxy-7-methyl-3,4,4*a*,5,6,9,10,11*a*-octahydro-1*H*-cyclonona[c]pyran-11-one (17*a*). **(3*R*,4*aR*,11*aS*)-3-Methoxy-7-methyl-3,4,4*a*,5,6,9,10,11*a*-octahydro-1*H*-cyclonona[c]pyran-11-one (17*b*).** NaH (76 mg, 3.14 mmol) was dissolved in 3.2 mL of DMSO, and the methylsulfinyl carbanion was prepared in the usual way.¹⁸ At room temperature, tosylate **14** (0.5 g, 1.21 mmol), dissolved in 3 mL of DMSO, was added while the color turned to brown. The reaction was quenched after 20 min by the addition of H₂O. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. Purification by flash chromatography (SiO₂, 3:2 hexane/EtOAc) afforded 175 mg (61%) of **17a** as a white solid and 82 mg (28%) of **17b** as a colorless oil. Crystals of **17a** suitable for X-ray structure determination were obtained from hexane/EtOAc. Data for **17a**: mp 77–79 °C; R_f 0.50 (3:2 hexane/EtOAc); $[\alpha]_D^{24} +64.5$ (c 1.40, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.28 (dt, $J = 3.8, 14.5$ Hz, 1H), 1.43 (m, 1H), 1.48 (m, 1H), 1.52 (s, 3H), 1.77 (ddd, $J = 2.3, 4.6, 13.8$ Hz, 1H), 1.95 (m, 2H), 2.02 (m, 1H), 2.06 (m, 1H), 2.20 (m, 1H), 2.31 (td, $J = 4.4, 11.5$ Hz, 1H), 2.59 (td, $J = 4.9, 11.2$ Hz, 1H), 2.69 (m, 1H), 3.36 (s, 3H), 3.40 (dd, $J = 4.4, 11.1$ Hz, 1H), 3.86 (t, $J = 11.3$ Hz, 1H), 4.63 (dd, $J = 2.6, 3.2$ Hz, 1H), 5.42 (dd, $J = 3.6, 11.2$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 17.22, 24.64, 31.67, 35.05, 37.29, 38.91, 39.22, 54.69, 59.10, 97.88, 124.15, 136.47, 213.01. Data for **17b**: R_f 0.37 (3:2 hexane/EtOAc); $[\alpha]_D^{23} -66.3$ (c 2.40, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 1.37 (td, $J = 9.2, 12.9$ Hz, 1H), 1.46–1.50 (m, 1H), 1.60 (s, 3H), 1.86 (ddd, $J = 3.3, 4.4, 13.6$ Hz, 1H), 1.99–2.03 (m, 3H), 2.12 (m, 1H), 2.23–2.33 (m, 3H), 2.48–2.57 (m, 1H), 2.64–2.79 (m, 1H), 3.45 (s, 3H), 3.53 (dd, $J = 8.1, 12.1$ Hz,

1H), 3.86 (dd, $J = 4.8, 12.1$ Hz, 1H), 4.48 (dd, $J = 3.3, 9.2$ Hz, 1H), 5.37 (dd, $J = 1.1, 4.8$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 16.97, 23.73, 34.67, 37.20, 38.75, 41.47, 55.95, 60.33, 62.66, 101.52, 123.96, 136.50, 212.89.

(4aR,11aS)-7-Methyl-1,4,4a,5,6,9,10,11a-octahydrocycloclonona[c]pyran-3,11-dione (18). NaH (8 mg, 0.33 mmol) was dissolved in 0.53 mL of DMSO, and the methylsulfinyl carbanion was prepared in the usual way. At room temperature, tosylate **16** (50 mg, 0.13 mmol) in 2 mL of DMSO was added. The reaction was quenched after 30 min by the addition of phosphate buffer (pH 7.0, $c(\text{KH}_2\text{PO}_4) = 0.026$ mol/L, $c(\text{Na}_2\text{HPO}_4) = 0.041$ mol/L). The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. Purification by flash chromatography (SiO_2 , 1:3 hexane/EtOAc) afforded 20 mg (71%) of enone **18** as a white solid. Crystals of **18** suitable for X-ray structure determination were obtained from MeOH. Data for **18**: mp 163 °C; R_f 0.56 (1:3 hexane/EtOAc); $[\alpha]_D^{25} +111$ (c 0.25, CHCl_3); IR 1706, 1753 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.57–1.63 (m, 2H), 1.82 (s, 3H), 2.03–2.13 (m, 1H), 2.21 (dt, $J = 3.7, 12.1$ Hz, 1H), 2.25–2.28 (m, 1H), 2.30–2.37 (m, 3H), 2.56–2.66 (m, 1H), 2.73 (ddd, $J = 4.0, 5.5, 9.9$ Hz, 1H), 2.84 (dd, $J = 7.4, 14.7$ Hz, 1H), 2.92 (dd, $J = 1.8, 9.9$ Hz, 1H), 3.98 (dd, $J = 9.9, 11.4$ Hz, 1H), 4.22 (dd, $J = 5.5, 11.4$ Hz, 1H), 5.27 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 16.52, 21.08, 36.13, 36.34, 36.37, 39.50, 40.18, 55.38, 66.50, 122.69, 138.29, 172.40, 213.67; MS (EI) m/z 222 (68), 55 (100).

(3RS,4aR,6aS,7R,9aR,9bS)-Toluene-4-sulfonic Acid 3,9a-dihydroxy-6a-methyl-dodecahydrocyclopenta[h]isochromen-7-yl Ester (19). To a cooled (-65 °C) solution of tosylate **16** (60 mg, 0.15 mmol) in 12 mL of CH_2Cl_2 was added dropwise DIBALH (0.19 mL, 1 M in THF, 0.19 mmol). After stirring for 30 min at this temperature, the reaction was quenched by the addition of 6 mL of MeOH followed by 6 mL of phosphate buffer (pH 7.0). The reaction mixture was stirred for 1 h at room temperature and then extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO_4), and evaporated to a volume of 20 mL. The residue was filtered through a 10 cm thick pad of SiO_2 with EtOAc. The solvent was evaporated and the crude product purified by flash chromatography (SiO_2 , EtOAc) to afford 59 mg (98%) of lactol **19** ($\alpha:\beta$ 1:1) as a white foam. Data for **19**: R_f 0.36 (EtOAc); IR 1358, 3446, 3609 cm^{-1} ; NMR signals for α -isomer indicated: ^1H NMR (300 MHz, CDCl_3) δ 0.80–0.90 (m, 1H), 0.91 (s, 3H), 1.04–1.06 (m, 1H), 1.17–1.18 (m, 1H), 1.20–1.35 (m, 1H), 1.25 (m, 1H), 1.45 (m, 1H), 1.58–1.63 (m, 1H), 1.65–1.68 (m, 1H), 1.80–1.84 (m, 2H), 1.80–1.90 (m, 1H), 2.45 (s, 3H), 3.39 (brs, 1H), 3.61 (dd, $J = 3.7, 11.4$ Hz, 1H), 3.96 (m, 1H), 4.68 (dd, $J = 2.2, 9.9$ Hz, 1H), 4.89 (m, 1H), 7.35 (d, $J = 7.7, 2\text{H}$), 7.79 (d, $J = 8.1, 2\text{H}$); ^{13}C NMR (75 MHz, CDCl_3) δ 16.77, 21.57, 28.49, 32.59, 33.26, 39.86, 44.96, 47.24, 59.09, 77.26, 81.51, 96.07, 127.73, 129.74, 133.96, 144.72; NMR signals for β -isomer indicated: ^1H NMR (300 MHz, CDCl_3) δ 0.80–0.90 (m, 1H), 0.91 (s, 3H), 1.08–1.12 (m, 1H), 1.20–1.35 (m, 1H), 1.25–1.35 (m, 1H), 1.28–1.45 (m, 2H), 1.68–1.75 (m, 1H), 1.77–1.80 (m, 2H), 1.88–1.92 (m, 1H), 1.90–1.95 (m, 1H), 2.45 (s, 3H), 2.95 (brs, 1H), 3.52 (dd, $J = 10.3, 11.4$ Hz, 1H), 4.01 (m, 1H), 4.83 (t, $J = 7.7$ Hz, 1H), 5.23 (d, $J = 2.9$ Hz, 1H), 7.35 (d, $J = 7.7, 2\text{H}$), 7.79 (d, $J = 8.1, 2\text{H}$); ^{13}C NMR (75 MHz, CDCl_3) δ 17.02, 21.57, 25.52, 27.50, 28.18, 28.65, 31.95, 37.38, 44.49, 66.01, 81.28, 91.30, 127.73, 129.74, 133.78, 144.75; MS (LSIMS) m/z 397 (11), 379 (100); HRLSIMS m/z calcd for $\text{C}_{20}\text{H}_{29}\text{O}_6\text{S}$ 397.1684, found 397.1685.

(3RS,4aR,11aS)-3-Hydroxy-7-methyl-3,4,4a,5,6,9,10,11a-octahydro-1H-cyclonona[c]pyran-11-one (20). To a solution of lactol **19** (20 mg, 50.4 μmol) in 0.3 mL of DMSO was added a solution of methylsulfinyl carbanion (0.22 mL, 0.17 mmol), prepared from 33 mg of NaH and 1 mL of DMSO in the usual manner, at room temperature under vigorous stirring. The mixture turned immediately to yellow and was stirred for 10 min while more methylsulfinyl carbanion (60 μL , 45.4 μmol) was added. The reaction was quenched with 10 mL of phosphate buffer (pH 7.0, $c(\text{KH}_2\text{PO}_4) = 0.026$ mol/L, $c(\text{Na}_2\text{HPO}_4) = 0.041$ mol/L). H_2O was added and the aqueous layer extracted with EtOAc. After drying (MgSO_4)

and evaporation of the solvent, the crude product was purified by flash chromatography (SiO_2 , EtOAc + 0.5% Et_3N) to yield 10 mg (88%) of enone **20** ($\alpha:\beta$ 56:44) as a white solid. Data for **20**: mp 102 °C; R_f 0.57 (EtOAc); IR 1692, 3620 cm^{-1} ; NMR signals for α -isomer indicated: ^1H NMR (300 MHz, CDCl_3) δ 1.40–1.42 (m, 2H), 1.64 (s, 3H), 1.67–1.69 (m, 1H), 1.85 (ddd, $J = 2.9, 4.8, 14.0$ Hz, 1H), 2.00–2.05 (m, 2H), 2.15–2.17 (m, 1H), 2.15–2.19 (m, 1H), 2.35–2.40 (m, 1H), 2.38–2.43 (m, 1H), 2.50–2.54 (m, 1H), 2.61–2.66 (m, 1H), 3.56 (dd, $J = 4.8, 11.8$ Hz, 1H), 3.98 (dd, $J = 8.5, 11.8$ Hz, 1H), 5.24 (q, $J = 2.9$ Hz, 1H), 5.39 (brdd, $J = 4.8, 11.4$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 16.97, 23.38, 30.56, 34.93, 36.33, 38.92, 39.37, 58.80, 60.12, 91.56, 123.37, 137.23, 214.85; NMR signals for β -isomer indicated: ^1H NMR (300 MHz, CDCl_3) δ 1.25–1.33 (m, 1H), 1.35–1.38 (m, 2H), 1.59 (s, 3H), 1.95–1.98 (m, 1H), 1.99–2.03 (m, 2H), 2.10–2.15 (m, 1H), 2.15–2.20 (m, 1H), 2.25–2.30 (m, 1H), 2.38–2.44 (m, 1H), 2.45–2.55 (m, 1H), 2.62–2.70 (m, 1H), 3.55–3.60 (m, 1H), 3.83 (dd, $J = 4.4, 11.8$ Hz, 1H), 4.85 (m, 1H), 5.39 (brdd, $J = 4.8, 11.4$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 17.23, 24.12, 29.56, 34.85, 38.79, 38.89, 39.50, 60.70, 64.02, 95.28, 124.11, 136.70, 213.03; MS (EI) m/z 224 (3), 67 (100); HREIMS m/z calcd for $\text{C}_{13}\text{H}_{20}\text{O}_3$ 224.1412, found 224.1412.

(3S,4aR,11aR)-3-Methoxy-7-methyl-11-methylene-1,3,4,4a,5,6,9,10,11,11a-decahydrocycloclonona[c]pyran (21a). A solution of MePPh_3Br (135 mg, 0.38 mmol) in 0.4 mL of THF was cooled to -30 °C, and $n\text{-BuLi}$ (0.23 mL, 1.6 M in hexane, 0.38 mmol) was slowly added to give an orange/yellow suspension. After stirring for 1 h at this temperature, a solution of methylacetal **17a** (45 mg, 0.19 mmol) in 0.2 mL of THF was added dropwise, and the suspension was allowed to warm to room temperature. After the suspension was stirred overnight (white suspension), H_2O was added and the aqueous layer extracted with Et_2O . The combined organic layers were dried (Na_2SO_4) and evaporated. Purification by flash chromatography (SiO_2 , 5:1 hexane/EtOAc) yielded 10 mg (23%) of diene **21a** as a colorless oil and 33 mg (73%) of starting material. Data for **21a**: R_f 0.52 (5:1 hexane/EtOAc); ^1H NMR (300 MHz, CDCl_3) δ 1.22–1.30 (m, 1H), 1.35–1.42 (m, 1H), 1.58 (s, 3H), 1.78–1.88 (m, 3H), 1.96–2.00 (m, 5H), 2.12–2.21 (m, 1H), 2.37 (dd, $J = 5.1, 11.4$ Hz, 1H), 3.30 (dd, $J = 4.1, 11.4$ Hz, 1H), 3.37 (s, 3H), 3.65 (t, $J = 11.4$ Hz, 1H), 4.64 (dd, $J = 2.2, 3.3$ Hz, 1H), 4.85 (s, 1H), 4.95 (s, 1H), 5.34 (dd, $J = 4.0, 11.7$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 16.10, 26.25, 29.54, 29.92, 33.14, 35.99, 36.95, 52.22, 60.55, 62.85, 95.93, 113.84, 122.17, 133.65, 146.99; MS (EI) m/z 236 (10), 28 (100).

(3R,4aR,11aR)-3-Methoxy-7-methyl-11-methylene-1,3,4,4a,5,6,9,10,11,11a-decahydrocycloclonona[c]pyran (21b). To a cooled solution (-40 °C) of methylacetal **17b** (60 mg, 0.25 mmol) in 1.5 mL of THF was added dropwise the Tebbe reagent (0.5 mL, 0.5 M in toluol, 0.25 mmol). The reaction mixture was allowed to warm to room temperature and stirred for another 4 h. The suspension was again cooled to -20 °C, and 0.3 mL of a 15% aqueous NaOH solution was added dropwise. THF (2 mL) was added, and stirring was continued for 10 h. The suspension was filtered through a pad of Celite and washed with EtOAc. The solvent was removed and purification by flash chromatography (SiO_2 , 3:1 to 5:1 hexane/EtOAc) afforded 22 mg (37%) of diene **21b** as a colorless oil. Data for **21b**: R_f 0.42 (5:1 hexane/EtOAc); ^1H NMR (300 MHz, CDCl_3) δ 1.31–1.39 (m, 2H), 1.58 (s, 3H), 1.76–1.78 (m, 1H), 1.82–1.85 (m, 1H), 1.86–1.91 (m, 1H), 1.93–2.08 (m, 5H), 2.12–2.23 (m, 1H), 2.37 (dd, $J = 4.8, 11.8$ Hz, 1H), 3.38 (t, $J = 11.8$ Hz, 1H), 3.47 (s, 3H), 3.71 (dd, $J = 4.4, 11.8$ Hz, 1H), 4.27 (dd, $J = 2.2, 9.6$ Hz, 1H), 4.87 (s, 1H), 4.96 (s, 1H), 5.27 (dd, $J = 5.5, 11.8$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 18.46, 31.58, 35.20, 35.90, 39.71, 54.76, 55.99, 102.78, 116.91, 124.36, 136.04, 148.04.

(4aR,11aR)-7-Methyl-11-methylene-4,4a,5,6,9,10,11,11a-octahydro-1H-cyclonona[c]pyran-3-one (22). To a solution of lactol **28** (60 mg, 0.27 mmol) in 2.5 mL of benzene was added Ag_2CO_3 on Celite (324 mg, 0.54 mmol). The suspension was heated for 30 min at 60 °C while the color turned to black. The mixture was filtered through a pad of Celite and washed with EtOAc. Evaporation of the solvent and purification by flash chromatography (SiO_2 , 2:1 hexane/EtOAc + 0.5% Et_3N)

afforded 53 mg (89%) of lactone **22** as a white solid. Crystals were obtained from hexane. Data for **22**: mp 44–45 °C; R_f 0.58 (2:1 hexane/EtOAc); $[\alpha]_D^{25} +159$ (c 0.70, CHCl₃); IR 1744, 3013, 3028 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.53–1.58 (m, 2H), 1.66 (d, J = 1.2 Hz, 3H), 1.87–1.92 (m, J = 1.0, 5.9, 10.0 Hz, 1H), 2.01–2.03 (m, 1H), 2.08–2.19 (m, 4H), 2.31–2.32 (m, 1H), 2.30–2.35 (dd, J = 4.1, 14.5 Hz, 1H), 2.41–2.47 (m, 1H), 2.79 (dd, J = 7.0, 14.5 Hz, 1H), 3.85 (ddd, J = 0.4, 10.0, 11.7 Hz, 1H), 4.11 (dd, J = 5.9, 11.7 Hz, 1H), 4.87 (s, 1H), 4.93 (s, 1H), 5.31 (brt, J = 7.8 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 16.34, 24.76, 35.26, 36.96, 37.27, 39.75, 40.78, 48.30, 70.72, 112.64, 124.32, 135.45, 152.70, 173.47; MS (EI) m/z 220 (34), 81 (100); HREIMS m/z calcd for C₁₄H₂₀O₂ 220.1463, found 220.1463; Anal. Calcd for C₁₄H₂₀O₂: C, 76.33; H, 9.15. Found: C, 76.33; H, 9.01.

1-Hydroxy-10-methyl-4-oxatricyclo[8.3.1.0^{2,7}]tetradecan-5-one (23a/b). Diene **21a** (30 mg, 0.13 mmol) was dissolved in 0.6 mL of THF, and 0.6 mL 0.5 M aqueous HCl was added. The mixture was heated to 60 °C and stirred for 24 h. EtOAc was added and the organic layer washed with saturated aqueous NaHCO₃ solution and brine, dried (Na₂SO₄), and evaporated. The crude product was dried under high vacuum overnight and directly dissolved in 1.5 mL of benzene. Ag₂CO₃ on Celite (0.7 g, 1.22 mmol) was added and the suspension heated to reflux for 3 h. Filtration through a pad of Celite, washing with EtOAc, evaporation, and purification by flash chromatography (SiO₂, 1:2 hexane/EtOAc) afforded 18 mg (61%) of **23a/b** (unseparable 1:1 mixture) as a colorless oil. Data for **23a/b**: R_f 0.58 (1:2 hexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 0.90 (s, 3H), 0.99 (s, 3H), 1.02–1.06 (m, 1H), 1.11–1.26 (m, 8H), 1.37–1.47 (m, 6H), 1.60–1.75 (m, 7H), 1.81–1.96 (m, 5H), 1.98–2.06 (m, 2H), 2.09–2.12 (m, 1H), 2.16–2.20 (m, 1H), 2.22–2.32 (m, 1H), 2.67 (dd, J = 5.2, 18.0 Hz, 1H), 2.75 (dd, J = 6.3, 15.8 Hz, 1H), 4.17 (t, J = 11.0 Hz, 1H), 4.23 (dd, J = 9.6, 11.8 Hz, 1H), 4.36 (dd, J = 4.4, 11.8 Hz, 1H), 4.67 (dd, J = 3.7, 10.7 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 19.40, 19.67, 29.40, 29.50, 31.18, 31.24, 32.16, 32.32, 32.87, 33.41, 34.05, 35.90, 36.62, 37.26, 37.79, 38.05, 38.24, 39.96, 41.16, 48.30, 50.25, 50.48, 68.33, 70.46, 71.49, 72.07, 170.03, 171.66; MS (LSIMS) m/z 239 (21), 133 (100).

(10S,17thioxy-1-oxadispiro[2.0.2.7]tridec-10-en-7-yl)-acetic Acid Methyl Ester (25). To a solution of trimethylsulfoxonium iodide (67 mg, 0.30 mmol) in 0.6 mL of DMSO was added a solution of *t*-BuOK (30 mg, 0.27 mmol) in 0.4 mL of DMSO. After stirring for 20 min, enone **18** (15 mg, 0.07 mmol) in 0.5 mL of DMSO was added. After heating at 60 °C for 24 h, a further portion of trimethylsulfoxonium iodide (67 mg, 0.30 mmol) in 0.6 mL of DMSO and *t*-BuOK (30 mg, 0.27 mmol) in 0.4 mL of DMSO (prepared as above) was added. Stirring and heating at 60 °C for further 24 h was continued. The reaction was quenched by the addition of phosphate buffer (pH 7.0). The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried (MgSO₄) and evaporated. Purification by flash chromatography (SiO₂, 3:2 hexane/EtOAc) afforded 5.5 mg (35%) of **25** as a colorless oil. Data for **25**: R_f 0.40 (3:1 hexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 0.47–0.54 (m, 1H), 0.60–0.67 (m, 1H), 0.74–0.81 (m, 1H), 1.25–1.30 (m, 1H), 1.40 (ddd, J = 4.8, 6.3, 10.7 Hz, 1H), 1.51 (s, 3H), 1.52–1.63 (m, 4H), 2.05–2.17 (m, 3H), 2.18–2.23 (m, 1H), 2.24–2.27 (m, 1H), 2.71 (td, J = 4.4, 11.8 Hz, 1H), 2.81–2.88 (m, 2H), 3.70 (s, 3H), 5.70 (dd, J = 3.3, 11.0 Hz, 1H); MS (EI) m/z 264 (1), 40 (100).

(3*R,S*,4*aR*,11*aS*)-3-(*tert*-Butyldimethylsilyloxy)-7-methyl-3,4,4*a*,5,6,9,10,11*a*-octahydro-1*H*-cyclonona[c]pyran-11-one (26). To a solution of lactol **20** (71 mg, 0.32 mmol) in 4.5 mL of CH₂Cl₂ was added imidazole (65 mg, 0.95 mmol) followed by TBDMSCl (96 mg, 0.63 mmol). After stirring for 29 h, H₂O was added. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried (Na₂SO₄), and evaporated. Purification by flash chromatography (SiO₂, 10:1 hexane/EtOAc + 0.5% Et₃N) afforded 105 mg (98%) of silylactal **26** (α : β 13:87) as a colorless oil. Data for **26**: R_f 0.39 (10:1 hexane/EtOAc); IR 1694 cm⁻¹; NMR signals for β -isomer indicated: ¹H NMR (300 MHz, CDCl₃) δ 0.11 (s, 6H), 0.90 (s, 9H), 1.35–1.42 (m, 1H), 1.40–

1.48 (m, 2H), 1.57 (s, 3H), 1.81–1.85 (m, 1H), 1.98–2.01 (m, 2H), 2.00–2.05 (m, 1H), 2.07–2.09 (m, 1H), 2.18–2.22 (m, 1H), 2.28 (td, J = 4.4, 9.9 Hz, 1H), 2.54 (td, J = 5.5, 11.4 Hz, 1H), 2.70–2.75 (m, 1H), 3.53 (dd, J = 9.9, 11.8 Hz, 1H), 3.84 (dd, J = 4.4, 11.8 Hz, 1H), 4.78 (dd, J = 2.6, 9.2 Hz, 1H), 5.39 (brdd, J = 3.3, 11.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ -5.19, -4.28, 17.36, 18.00, 24.32, 25.72, 34.83, 35.79, 38.75, 38.92, 41.12, 61.05, 64.40, 96.08, 124.18, 136.71, 213.12; MS (LSIMS) m/z 337 (45), 133 (100).

(3*R,S*,4*aR*,11*aR*)-*tert*-Butyldimethyl-(7-methyl-11-methylene-1,3,4,4*a*,5,6,9,10,11,11*a*-decahydrocyclonona[c]pyran-3-yloxy)silane (27). A solution of silylactal **26** (82 mg, 0.24 mmol) in 2 mL of THF and 0.14 mL of pyridine at -5 °C was treated with Tebbe reagent (0.67 mL, 0.5 M in toluene, 0.336 mmol). The solution was allowed to warm to room temperature over a period of 30 min. After 1.5 h, the solution was cooled (0 °C) and stirred vigorously, and 5 mL of THF was added, followed by careful addition of 2 mL of 15% aqueous NaOH solution. The deep red suspension was stirred for 1 h, MgSO₄ was added, and stirring was continued for further 30 min. It was filtered through a pad of Celite and washed with EtOAc. Evaporation of the solvent yielded a red/brown oil which was filtered through a column (Al₂O₃ neutral II, 30:1 hexane/EtOAc) to give a yellow oil. Purification by flash chromatography (SiO₂, 30:1 hexane/EtOAc + 0.5% Et₃N) afforded 57 mg (70%) of diene **27** (α : β 5:95) as a slightly yellow oil. Data for **27**: R_f 0.54 (30:1 hexane/EtOAc); IR 3015, 3028 cm⁻¹; NMR signals for β -isomer indicated: ¹H NMR (500 MHz, CDCl₃) δ 0.14 (s, 6H), 0.93 (s, 9H), 1.36–1.38 (m, 1H), 1.42–1.44 (m, 1H), 1.60 (s, 3H), 1.75–1.79 (m, 1H), 1.81–1.82 (m, 1H), 1.83 (ddd, J = 2.1, 4.4, 12.8 Hz, 1H), 1.96–1.99 (m, 2H), 1.97–1.99 (m, 2H), 2.03–2.06 (m, 1H), 2.20 (dbrt, J = 13.3 Hz, 1H), 2.38 (dd, J = 4.9, 12.0 Hz, 1H), 3.38 (t, J = 11.5 Hz, 1H), 3.68 (dd, J = 4.4, 11.7 Hz, 1H), 4.65 (dd, J = 2.1, 9.3 Hz, 1H), 4.88 (d, J = 1.5 Hz, 1H), 4.97 (d, J = 1.7 Hz, 1H), 5.31 (dd, J = 5.4, 11.7 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ -5.16, -4.18, 18.04, 18.47, 25.77, 28.66, 31.52, 35.20, 36.22, 39.13, 42.86, 54.68, 69.27, 96.64, 116.87, 124.33, 136.06, 147.79; MS (LSIMS) m/z 337 (9), 161 (100); HREIMS m/z calcd for C₂₀H₃₆O₂Si 337.2562, found 337.2560.

(3*R,S*,4*aR*,11*aR*)-7-Methyl-11-methylene-1,3,4,4*a*,5,6,9,10,11,11*a*-decahydrocyclonona[c]pyran-3-ol (28). To a solution of diene **27** (106 mg, 0.31 mmol) in 3.5 mL of THF was added TBAF (0.47 mL, 1 M in THF, 0.47 mmol). After stirring for 4 h, H₂O was added. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried (MgSO₄), and evaporated. Purification by flash chromatography (SiO₂, 1:1 hexane/EtOAc + 0.5% Et₃N) afforded 60 mg (85%) of lactol **28** (α : β 47:53) as a colorless oil. Data for **28**: R_f 0.46 (1:1 hexane/EtOAc); IR 2929, 3007, 3595 cm⁻¹; NMR signals for β -isomer indicated: ¹H NMR (300 MHz, CDCl₃) δ 1.59 (s, 3H), 1.22–2.55 (m, 13H), 3.33 (dd, J = 4.4, 11.4 Hz, 1H), 3.89 (t, J = 11.4 Hz, 1H), 4.68 (dd, J = 1.8, 2.2 Hz, 1H), 4.88 (s, 1H), 4.97 (d, J = 1.1 Hz, 1H), 5.34 (m, 1H); MS (EI) m/z 222 (2), 41 (100); HREIMS m/z calcd for C₁₄H₂₂O₂ 222.1619, found 222.1622.

(4*S*,4*aS*,11*aR*)-7-Methyl-11-methylene-4-(4-methylpent-2-enyl)-4,4*a*,5,6,9,10,11,11*a*-octahydro-1*H*-cyclonona[c]pyran-3-one (1a). **(4*R*,4*aS*,11*aR*)-7-Methyl-11-methylene-4-(4-methylpent-2-enyl)-4,4*a*,5,6,9,10,11,11*a*-octahydro-1*H*-cyclonona[c]pyran-3-one (1b).** A solution of diisopropylamine (DIPA) (59.7 μ L, 0.42 mmol) in 0.63 mL of 2:1 THF/1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) was cooled to -35 °C, and *n*-BuLi (255 μ L, 1.6 M in hexane, 0.41 mmol) was added dropwise. After the mixture was stirred for 5 min, the dry ice–2-propanol bath was replaced by an ice bath, and the mixture was stirred for 30 min. From this solution was taken 315 μ L and recooled to -78 °C. Lactone **22** (10 mg, 45.4 μ mol), dissolved in 0.15 mL of THF, was added dropwise, and the reaction mixture was stirred for 1 h. 1-Bromo-4-methylpent-2-ene (7.3 μ L, 54.5 μ mol) (in a 4:1 mixture with 3-bromo-4-methylpent-1-ene) was added. The reaction mixture was stirred for 10 min and then left for 17 h at -68 °C. Quenching with 5 mL of saturated aqueous NaHCO₃ solution at -68 °C followed by extraction with Et₂O

afforded after drying (MgSO_4) and purification by flash chromatography (SiO_2 , 2:1 hexane/EtOAc + 0.5% Et_3N) 5.8 mg (42%) of 4-*epi*-coraxeniolide-A (**1b**) and 1.0 mg (7%) of coraxeniolide-A (**1a**) as colorless oils, together with 3.0 mg (30%) of unreacted starting material **22**. Crystals of **1a** suitable for X-ray structure determination were obtained from CH_2Cl_2 at 5 °C. Data for coraxeniolide-A (**1a**): R_f 0.63 (2:1 hexane/EtOAc); $[\alpha]^{22}_{\text{D}} + 72.0$ (c 0.47, CHCl_3); IR 1740, 3011, 3028 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.97 (dd, $J = 1.6, 6.8$ Hz, 6H), 1.03 (ddd, $J = 2.7, 3.2, 13.1$ Hz, 1H), 1.66 (d, $J = 1.2, 3\text{H}$), 1.71 (ddd, $J = 3.5, 3.6, 14.0$, 1H), 1.92 (td, $J = 4.4, 12.6$, 1H), 1.97–2.02 (m, 1H), 2.03–2.05 (m, 1H), 2.05–2.07 (m, 1H), 2.07–2.11 (m, 1H), 2.14–2.16 (m, 1H), 2.18–2.20 (m, 1H), 2.24 (dd, $J = 6.8, 13.5$ Hz, 1H), 2.30–2.34 (m, 1H), 2.43–2.47 (m, 1H), 2.52–2.59 (m, 1H), 2.77–2.83 (m, $J = 6.1, 14.2$ Hz, 1H), 3.90 (t, $J = 11.7$ Hz, 1H), 4.15 (dd, $J = 6.9, 11.7$ Hz, 1H), 4.94 (s, 1H), 4.95 (s, 1H), 5.28–5.32 (m, 2H), 5.47 (dd, $J = 6.8, 15.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.38, 22.58, 24.92, 29.59, 29.89, 31.06, 35.54, 39.55, 42.67, 44.06, 49.61, 70.56, 112.04, 123.26, 123.79, 135.90, 140.61, 152.98, 175.15; MS (EI) m/z 302 (10), 41 (100); HREIMS m/z calcd for $\text{C}_{20}\text{H}_{30}\text{O}_2$ 302.2245, found 302.2247. Data for 4-*epi*-coraxeniolide-A (**1b**): R_f 0.59 (2:1 hexane/EtOAc); $[\alpha]^{22}_{\text{D}} - 25.6$ (c 0.22, CHCl_3); IR 1735, 3011, 3028 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.96 (dd, $J = 1.6, 6.8$ Hz, 6H), 1.39–1.49 (m, 1H), 1.66 (d, $J = 1.3$ Hz, 3H), 1.71–1.73 (m, 1H), 1.75–1.78 (m, 1H), 1.82 (td, $J = 7.4, 10.0$ Hz, 1H), 1.99–2.05 (m, 3H), 2.17 (dt, $J = 3.6, 12.4$ Hz, 1H), 2.21–2.24 (m, 1H), 2.25–2.30 (m, 2H), 2.32 (dd, $J = 7.1, 13.5$ Hz, 1H), 2.40–2.48 (m, 1H), 2.50–2.53 (m, 1H), 3.98 (ddd, $J = 0.5, 2.6, 11.3$ Hz, 1H), 4.14 (dd, $J = 3.5, 11.3$ Hz,

1H), 4.68 (s, 1H), 4.86 (s, 1H), 5.30 (brt, $J = 7.4$ Hz, 1H), 5.43 (dd, $J = 5.4, 15.4$ Hz, 1H), 5.47–5.52 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.46, 22.64, 22.67, 25.07, 31.09, 31.53, 34.68, 35.17, 39.64, 43.81, 44.90, 48.84, 66.97, 113.37, 123.76, 124.49, 135.43, 141.04, 152.70, 175.00; MS (EI) m/z 302 (16), 41 (100); HREIMS m/z calcd for $\text{C}_{20}\text{H}_{30}\text{O}_2$ 302.2245, found 302.2244.

Epimerization of 4-*epi*-Coraxeniolide-A (1b**).** A solution of **1b** (5 mg, 16.5 μmol) in 0.1 mL of toluene was treated with a solution of TBD (5 mg, 35.9 μmol) in 0.04 mL of toluene at room temperature. The reaction was stirred for 5 min and left for 18 h. A small amount of saturated aqueous NaHCO_3 solution was added to the mixture, followed by dilution of EtOAc and direct drying over MgSO_4 . Filtration, evaporation, and purification by flash chromatography (SiO_2 , 3:1 hexane/EtOAc + 0.5% Et_3N) provided 3 mg (60%) of **1a** and 1 mg (20%) of **1b**.

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Supporting Information Available: ^1H NMR spectra for **1a**, **1b**, **4–28** and crystallographic data for **8**, **17a**, **18**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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