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A General Synthetic Approach to Optically Active Iridoid Aglycones. The Total Syntheses of β-Ethyl Descarbomethoxyverbenalol, Ethyl Catalpol, and (–)-Specionin+

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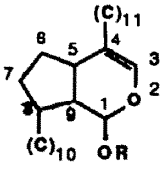
Abstract: *A general approach to the synthesis of iridoid aglycones is reported. A combination Claisen rearrangement/nitrile oxide cycloaddition sequence has permitted the facile annulation of a highly functionalized cyclopentane ring onto a simple glycal derived from D-xylal. The title aglycones have been prepared and the work has culminated with a stereoselective total synthesis of (–)-specionin. Two other anomers of specionin have also been independently prepared. The work confirms Vandewalle's relative stereochemical assignment of specionin and also confirms the absolute stereochemistry of this compound.*

Introduction

The iridoids are a large family of natural products which are characterized by a highly oxygenated, fused cyclopentapyran ring system (**1**).[2] Iridoid structures are conveniently grouped by the number and location of carbon atoms. Most iridoids belong to one of two groups:[3] one group has a ten carbon nucleus which contains both C-10 and C-11 [represented by verbenalin (**2**)], while the other has a nine carbon nucleus which contains C-10 but lacks C-11 [represented by catalpol and catalposide (**3a**, **3b**)]. Within these groups, there is a great diversity in location, oxidation state, and stereochemistry of oxygen functionality. Most naturally occurring iridoids have a β-non-reducing link to a sugar (often glucose) at C1 and a double bond at C3-C4. Iridoids such as catalpol, which lack the electron withdrawing group at C4, are often difficult to hydrolyze without decomposition due to the instability of this enol acetal.



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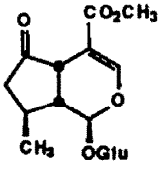
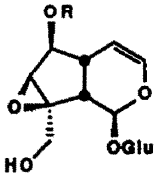
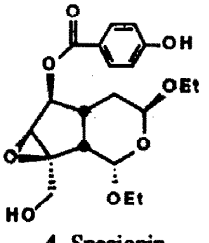


2 Verbenalin



3a Catalpol, R=H
3b Catalposide, R=C(O)C$_6$H$_4$OH



4 Specionin

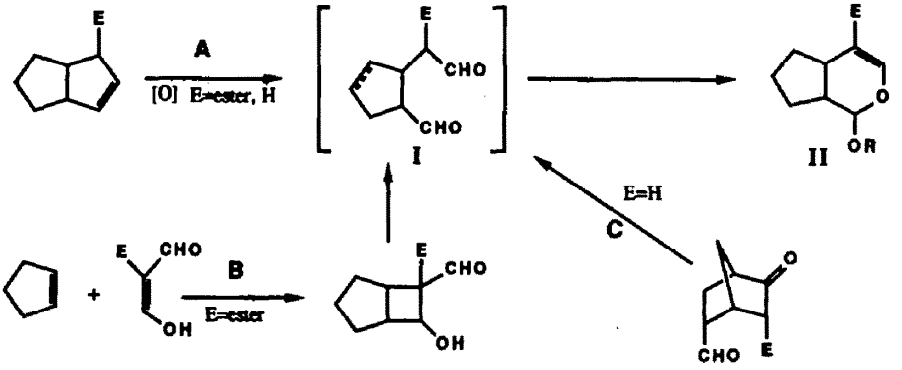
Certain iridoids are central intermediates in the biosynthesis of many of the important families of plant-derived alkaloids. In addition, many iridoids themselves possess interesting biological activities ranging from sedative to antimicrobial to antileukemic effects.[4] Specionin (**4**) is a recently discovered compound which has attracted much interest due to its potent antifeedant activity against the Eastern spruce budworm, a common pest in North American forests.[5a,b] Even though specionin (**4**) may be an artifact of isolation derived from the ethanolysis of catalposide (**3b**),[5c] its potent biological activity, combined with uncertainties in its structural assignment, has generated substantial synthetic interest.

In Scheme 1, key elements to some of the most common strategic approaches to iridoids are summarized.[6] Most past syntheses have capitalized on the synthetic equivalence of the dialdehyde (I) and the cyclopentapyran (II). This transformation (I → II) is directly related to the accepted pathway for the biosynthesis of iridoids from iridodial.[2] General methods to prepare derivatives related to (I) include the oxidative cleavage of fused cyclopentenes (path A, pioneered by Büchi[7]), enol [2+2] cycloaddition/retro-

+Dedicated to Professor Edward C. Taylor on the occasion of his 65th birthday.

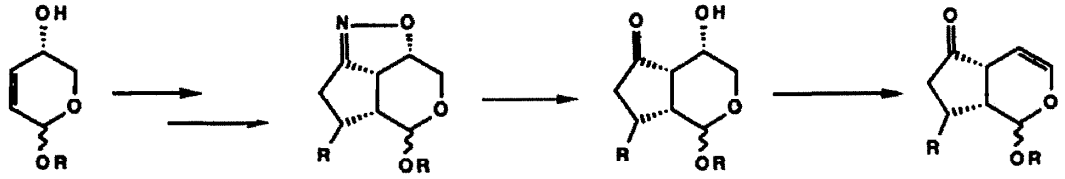
aldol cleavage (path B, pioneered by Büchi and Tietze[8]), and the more recent Norrish I cleavage of norbornanones (path C, pioneered by Vandewalle[9]). Such methods have proven to be very general, although not without limitations. Since the dialdehyde I is usually closed to II under thermodynamic conditions, control of stereochemistry at the anomeric position(s) may be limited. In addition, in the large class of iridoids where the C-11 ester is not present to facilitate enolization, formation of the sensitive enol acetal is not trivial.[10] Several Diels-Alder based strategies also provide access to derivatives of II.[11]

Scheme 1



The key elements of our new strategic approach to the iridoid family are outlined in Scheme 2. Our approach targets the less readily available class of iridoids which lack the stabilizing C-11 carbomethoxy group. Optically active glycal **i** is readily available from D-xylal. Our recent combination Claisen rearrangement/nitrile oxide cycloaddition method[12] provides an ideal sequence to fuse a highly functionalized cyclopentane ring to the glycal **i** to provide **ii** with rigorous control of stereochemistry. Standard reduction of **ii** produces **iii**. The development of a mild method to convert **iii** into the sensitive enol acetal **iv** was one of the important goals of this research.

Scheme 2



Results and Discussion

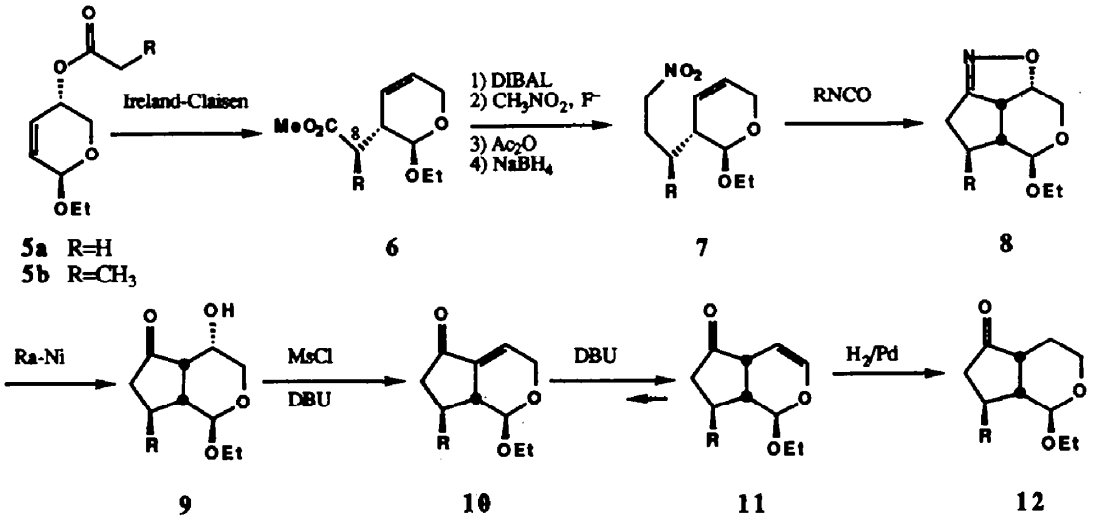
Preliminary Studies: Earlier work[12] had demonstrated the Claisen rearrangement/nitrile oxide cycloaddition sequence to be a useful, stereocontrolled annulation procedure in carbocyclic ring systems; it remained to demonstrate the usefulness of this approach with heterocyclic examples. The annulation of a cyclopentane ring onto an optically active, sugar-derived pyran ring was investigated as a model for the synthesis of compounds of the iridoid family (Scheme 3).

Glycal **5a** was prepared by Ferrier rearrangement of D-xylal[13] as described by Fraser-Reid.[14] The ratio of α/β anomers was 1/2.8. By HPLC separation and reequilibration of the undesired product, either anomer could be obtained in multigram quantities. For most of the work, the major β-anomer was employed. Ireland-Claisen rearrangement[15] and methylation of **5aβ** provided a 66% yield of **6a** as a single stereoisomer. After DIBAL reduction (60%) of **6a** to an aldehyde, Wollenberg homologation[16] (81%) provided the nitro olefin **7a**. This simple one flask sequence involves a Henry reaction followed by acetylation of the alcohol, elimination, and conjugate reduction. After intramolecular nitrile oxide cycloaddition[17] of **7a** under Mukaiyama conditions[18] (47%), Raney nickel reduction[19] of the Δ^2-isoxazoline **8a** provided the β-hydroxy ketone **9a** as the sole product in 82% yield.

We were now prepared to address the problem of formation of the enol acetal. Mesylation of **9a** with methanesulfonyl chloride gave the expected mesylate. Exposure of this mesylate to DBU first produced the α,β-unsaturated ketone **10a** in 87% yield. Upon continued exposure to DBU in CH_2Cl_2 (18 h, 25 °C), **10a** was smoothly deconjugated to the more stable β,γ-unsaturated ketone **11a** (> 95:5) in 79% yield. The equilibration was followed with NMR by observing the disappearance of the conjugated

enone proton at δ 6.28 ppm (C_6D_6) and the appearance of the enol ether protons at 4.73 and 6.07 ppm (C_6D_6). It was anticipated that **11** would be favored at equilibrium relative to **10** since, although enone resonance is lost, enol acetal resonance is gained and the strain accompanying the double bond exocyclic to the cyclopentane ring is removed.[20] Models indicated the trans-ring fused isomer of **11** to be much more strained than the cis.

Scheme 3



5a R=H
5b R=CH_3

6 **7** **8** **9** **10** **11** **12**

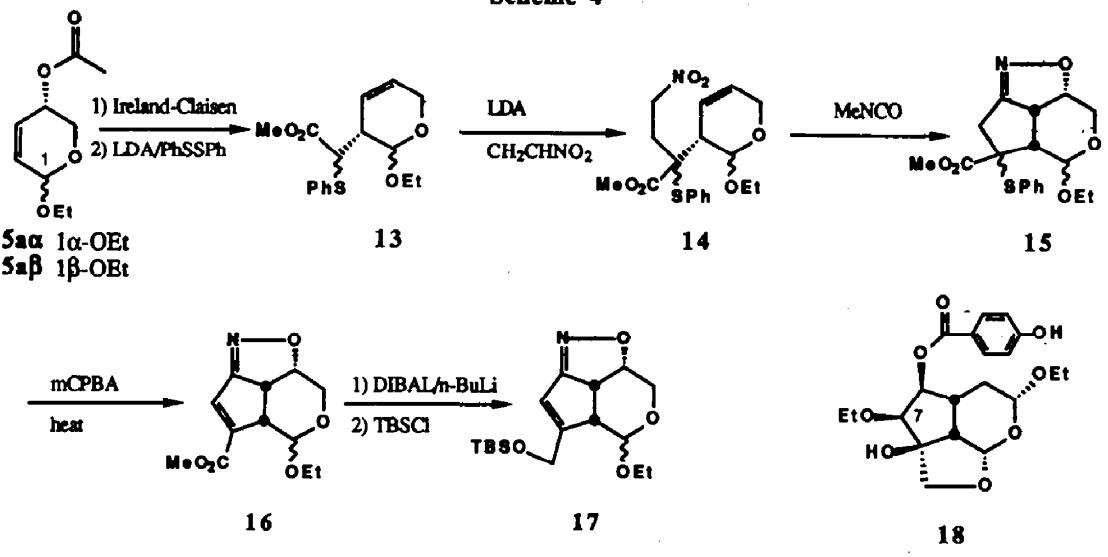
This model study had shown that the Claisen rearrangement/nitrile oxide cycloaddition sequence was excellent for annulation onto a sugar-derived ring, and that the β-hydroxy ketone was a useful precursor to the β,γ-enone. The remaining objective was the introduction of a substituent at C-8 in the cyclopentane ring (Scheme 3). For this purpose, the propionate **5b** was prepared in 67% yield from the acetate **5a** by standard ester enolate alkylation.

The best stereoselectivity in the Ireland-Claisen rearrangement was obtained by generation of the *E*-ketenesilyl acetal (LiN(TMS)$_2$, TBSCl) and subsequent rearrangement. This proceeded with reasonable selectivity through a chair-like transition state[21] to give **6b** and its diastereoisomer in a 5:1 ratio. The rearrangement of the *Z*-ketenesilyl acetal derived from **5b** also provided **6b** as the major isomer (now via a boat-like TS) but the ratio was only 3:2.[22] In the actual synthetic sequence, the crude acid produced by desilylation (K_2CO_3, MeOH/THF/H_2O) was directly reduced and oxidized to provide an aldehyde in 53% yield from **5b**. The subsequent Wollenberg homologation (66%), nitrile oxide cycloaddition (60%), and reduction (88%) proceeded to give the β-hydroxy ketone **9b**.

The synthesis of ethyl descarbomethoxy verbenalol (**11b**) was completed by mesylation, β-elimination, and equilibration of the α,β-unsaturated intermediate **10b** with DBU. This produced a single deconjugated product **11b** which retained the cis-fusion between the two rings. Evidence for this was provided by the magnitude of the coupling constant between the acetal proton and the adjacent ring fusion proton, $J_{1,9} = 2$ Hz. From Dreiding models it can be seen that, in the cis-fused compound, the β-ethoxy group must be in an axial-like position. The angle between these two protons approaches 90°. Models of the trans ring fusion isomer indicate a significantly larger dihedral angle. Both **11a** and **11b** rapidly decomposed on standing at room temperature over several days. For the purposes of characterization, **11b** was reduced with hydrogen gas in the presence of palladium on carbon to form **12b**.

Specionin (The Original Structure): As the model studies were nearing completion, our attention was attracted to a report by Nakanishi and Chang on the isolation of specionin from the leaves of the *catalpa speciosa* Warder tree.[5a,b] The structure of specionin was initially assigned as depicted in **18** (Scheme 4). These workers proposed that specionin might be derived from catalposide **3b** as an artifact of the ethanol isolation.[5c] While the formation of the cyclic acetal and the ethyl acetal at C1 and C3 are both reasonable and precedented possibilities, a simple method for the introduction of the C7 β-ethoxy group is not readily envisioned. Because of the interesting structure and biological activity of specionin, we selected structure **18** as a target to illustrate the utility of our synthetic strategy. Although specionin does not contain the enol acetal, we planned to use this functionality to introduce the C3 ethoxy group.

Scheme 4



5aα 1α-OEt
5aβ 1β-OEt

13 **14** **15**

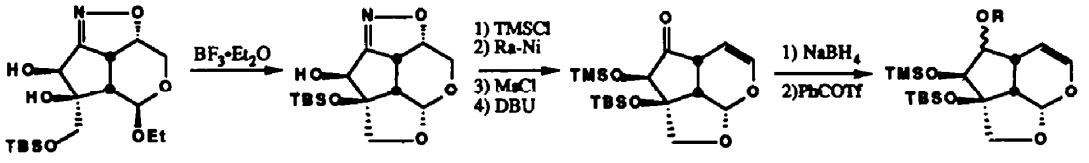
16 **17** **18**

The synthesis began with the previously prepared Ireland-Claisen rearrangement product **6a**. This methyl ester was sulfenylated with LDA and diphenyl disulfide (–25 °C to 25 °C) in THF according to the procedure used by Trost.[23] After flash chromatography, a 1:1 diastereomeric mixture of **13β** was isolated in 70% yield. The C8 stereogenic center was short-lived and the stereoisomeric mixtures did not pose a problem. Introduction of the nitroethyl group was achieved by addition of **13β** to LDA at –78 °C, followed by addition of freshly distilled nitroethylene.[24] The nitro compound **14β** was obtained as a 1.5:1 diastereomeric mixture in 90% yield. Intramolecular nitrile oxide cycloaddition of **14β** with methyl isocyanate and triethylamine provided a diastereomeric mixture of Δ^2-isoxazolines **15β** in nearly quantitative yield. Oxidation of **15β** with mCPBA at 0 °C went smoothly to give the presumed α-sulfinyl ester. Upon workup, the eliminated product **16β**, admixed with two diastereomers of the sulfinyl ester, was isolated. The above mixture was heated at 80 °C for 3 h to complete the elimination. This provided the tricyclic vinyl Δ^2-isoxazoline **16β** as a single stereoisomer in 59% yield.

A selective reduction of the C10 ester of the conjugated system of **16β** was now needed. After several unsuccessful attempts, it was found that when an aluminate complex[25] of DIBAL and *n*-butyllithium at –78 °C in THF was stirred with **16β** for 1 h, the required alcohol was obtained in 83% yield. No reduction of the C7-C8 double bond or the Δ^2-isoxazoline ring was observed. The crude primary alcohol was directly silylated with TBSCl to afford **17β** in 52% yield.

After the failure of a variety of catalytic osmylation procedures, the C7,C8 diol of the originally proposed structure of specionin **18** was introduced by stoichiometric osmylation[26] (Scheme 5). Cleavage of the osmate ester-pyridine complex with aqueous Na_2SO_3 and $KHCO_3$ in THF for 2 h gave the diol **19** in 80% yield. In an abortive attempt to protect the cis-diol, a useful transformation was discovered. Treatment of **19** with dimethylsilylditriflate and 2,6-lutidine provided not the expected cyclic silyl derivative but instead **20** in rather low yield. This transformation involves acetal exchange and selective migration of the TBS group to the neighboring 3°-alcohol. This discovery seemed ideally suited for the planned subsequent transformations. Unfortunately, optimized conditions (BF_3•Et_2O, CH_2Cl_2, 0 °C, 20 min) provided **20** in only 30% yield.

Scheme 5



19 **20** **21**

22a R=H
22b R=C(O)C_6H_5

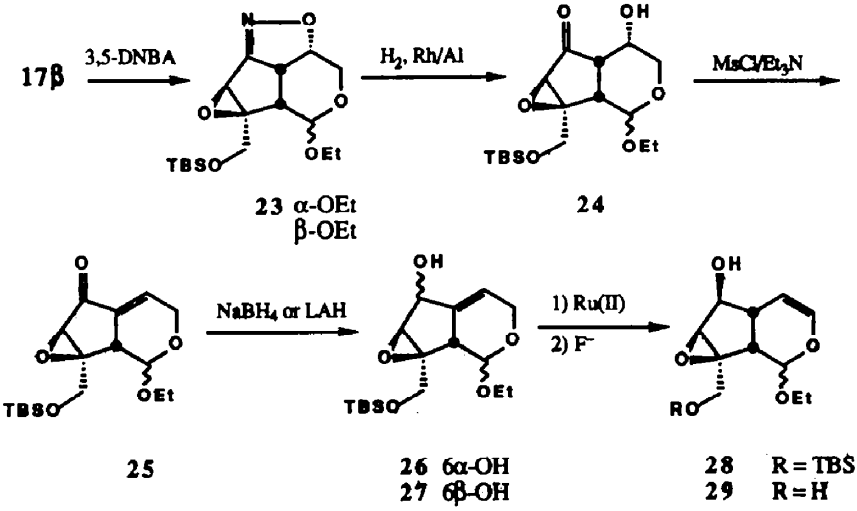
Continuing the synthesis, the secondary alcohol of **20** was first silylated. Next, Raney nickel-catalyzed reduction, followed by the mesylation/elimination/deconjugation sequence described above, proceeded smoothly to give the β,γ-unsaturated ketone **21** in good overall yield. We then began preliminary experiments to solve the final problems of the synthesis. It was first discovered that *O*-ethylation of the C7 hydroxyl group of **19** was possible (Meerwein's salt, CH_2Cl_2, 9 days). Furthermore, sodium borohydride reduction of **21** in THF/ethanol resulted in a 40% yield of the hydroxy compound **22a** as a single product after chromatography. Benzoylated product **22b** was obtained in 90% yield with benzoyl triflate and pyridine in methylene chloride.[27] Although the stereochemistry of the hydroxy group was not assigned, in retrospect (see below), it was probably α.

Specionin (The Correct Structure): At this point in the synthetic work, concerns about the validity of the structural assignment of specionin were confirmed by Vandewalle and co-workers.[28] This group prepared **18** via the norbornanone method and clearly showed that it was not identical to specionin. They also proposed the revised structure **4**. At this juncture, the anomeric stereochemistry (at C1 and C3) of specionin was unclear. Since specionin was proposed to arise from catalpol by ethanolysis during isolation, we felt that it was likely (although not definite) that it should be one of the most stable stereoisomers. In reviewing molecular models of the four possible diastereomers, we felt that two isomers were relatively unlikely. Assuming a chair-like conformation of the pyran ring, the α-C1,α-C3 isomer has both ethoxy groups axial while the the β-C1,β-C3 isomer has both ethoxy groups equatorial.[29] The former suffers severe 1,3-dipole repulsion while the latter lacks anomeric stabilization.[30] Either of the two trans isomers seemed reasonable at this point and it was difficult to select between the two since it was unclear which anomeric center had initially been assigned the incorrect stereochemistry in **18**.

Our synthetic strategy was sufficiently general so that one of our advanced intermediates, the Δ^2-isoxazoline **17β**, was ideal for the synthesis of the newly proposed structure of specionin **4** (anomeric stereochemistry unknown), as well as for the synthesis of ethyl catalpol. Since all our work had been in the β-C1 series, we elected first to prepare the β-C1,α-C3 isomer. Of course, equilibration to the most stable products might be accomplished at the end of the synthesis. Alterations in the synthetic plan involved epoxidation of the double bond of **17β** instead of osmylation, and omission of the cyclization step.

Epoxidation of the Δ^2-isoxazoline **17β** with 3,5-dinitroperoxybenzoic acid (3,5-DNBA),[31] 4,4-thiobis(2-*t*-butyl-6-methylphenol),[32] and sodium phosphate (monobasic) buffer in methylene chloride proceeded in quantitative yield to give the epoxy-isoxazoline **23β** (Scheme 6). The direction of approach of the epoxidizing agent was dictated by the convex shape of the tricyclic isoxazoline.

Scheme 6



Disappointingly, it was then found that Raney nickel reduction of the epoxy-isoxazoline **23β** under standard conditions resulted in decomposition of the starting material. Other reduction catalysts including palladium on carbon, platinum oxide, and rhodium on alumina (5%) under hydrogen atmosphere (boric acid, 5:1 methanol/water) were surveyed.[19] Only reduction with rhodium on alumina successfully afforded the desired β-hydroxy ketone **24β** (70% yield).

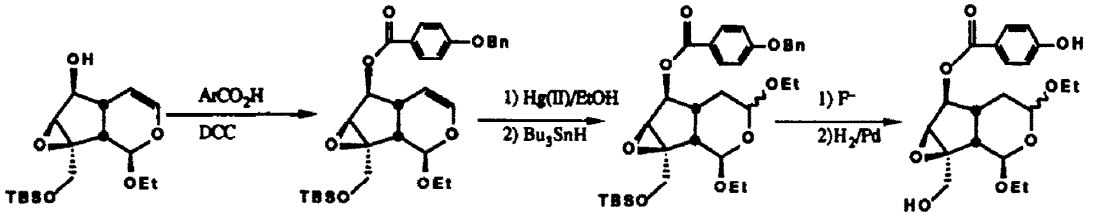
Continuing as before, the mesylation/elimination sequence provided the α,β-unsaturated ketone **25β** in quantitative yield; however, another obstacle quickly arose. Deconjugation of **25β** with DBU to the β,γ-unsaturated ketone, which occurred so readily in model systems, resulted only in decomposition. The same result was obtained with a variety of other bases including LDA, potassium *t*-butoxide, and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). A new method for generation of the enol acetal was required.

It was soon found that reduction of the enone **25β** to the α- or β-hydroxy epimer at C6 could be controlled by choice of reducing agent. The α-epimer **26β** was the major product (approximately 8:1) of reduction with sodium borohydride and cerium (III) chloride in methanol at 25 °C.[33] Reduction of **25β** with LAH[34] in ether at -78 °C provided predominantly the β-epimer **27β** (3:1). The α-epimer **26β** was isolated as a crystalline solid and an x-ray structure was obtained,[35] confirming all stereochemistry up to this point. Double bond migration was now attempted employing transition metal catalysts. Treatment of the requisite epimer **27β** with dihydridotetrakis(triphenylphosphine)ruthenium (II) in ethanol provided the desired enol acetal **28β** in 90% yield.[36]

Desilylation of **28β** with tetra-*n*-butylammonium fluoride in THF completed a synthesis of the aglycone of catalpol (**29β**, ethyl catalpol). As far as we know, this is the first synthesis of any aglycone derivative of catalpol. This product was made in optically active form in thirteen steps from **5β** in 8% overall yield.

The next step towards the synthesis of specionin was the *p*-benzyloxybenzoylation of the C6 hydroxyl (Scheme 7). Dicyclohexylcarbodiimide (DCC) coupling[37] of **28β** with *p*-benzyloxybenzoic acid and catalytic amount of DMAP in methylene chloride provided **30β** in quantitative yield. Among the various methods attempted to introduce the C3 ethoxy group, an oxymercuration/demercuration sequence was most successful.[38] Ethoxymercuration of **30β** with mercury (II) acetate in ethanol afforded a 1:1 mixture of **31β** and **32β** in 60% total yield after reductive demercuration. Desilylation of the above mixture was effected with tetra-*n*-butylammonium fluoride trihydrate in THF. The isomers were separated by MPLC, and debenzylation over palladium on carbon afforded the two pure products **33β**, **34β** in 86% and 89% yield, respectively. Structural assignments of these two anomers could readily be made by coupling constant analysis.[29]

Scheme 7



28β **30β** **31β** 3α-OEt **32β** 3β-OEt **33β** 3α-OEt **34β** 3β-OEt

Unfortunately, neither **33β** nor **34β** was identical with specionin. This convinced us that specionin must be **4**. At this time, Professor Vandewalle kindly informed us that he had completed a synthesis of all four diastereomers of specionin, along with a set of four more (minor) diastereomers epimeric at the epoxide-bearing carbons.[39] In a synthetic and spectroscopic tour-de-force, these isomers where later separated and each structure was assigned. Our structures **33β** and **34β** were identical with the appropriate purified components of the Vandewalle mixture.

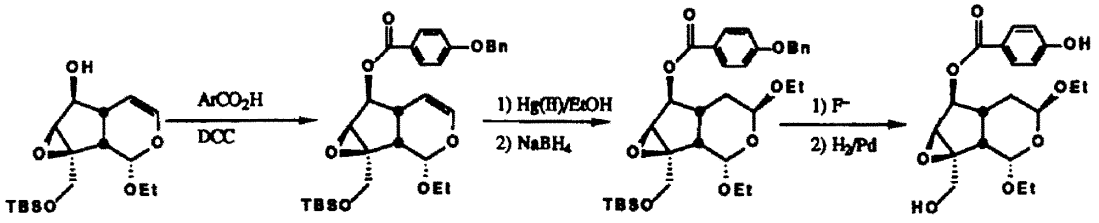
A preliminary experiment on possible equilibration seemed encouraging. Treatment of a sub-milligram quantity of **34β** with BF_3•OEt_2 in ethanol (2 days) provided a mixture which was characterized only by analytical HPLC. The major product of this mixture co-eluted with authentic specionin while the two minor products co-eluted with **33β** and **34β**. The presence of the fourth diastereomer was not obvious. We should emphasize that we have no evidence that the equilibration was actually complete;

however, similar results have been recently reported by Vandewalle and co-workers in a careful study of this equilibrium.[40]

This experiment suggested that specionin was indeed the thermodynamic product; however, we were far from confident that we could claim a total synthesis. Since we had nearly exhausted all our synthetic intermediates in the β-series, we were required to return to the beginning of the synthesis. We elected to repeat the synthesis starting with correct α-C1 isomer to obviate the need for equilibration and to provide rigorous proof of the structure of specionin.

We have recently communicated this total synthesis of (–)-specionin.[41] Starting with the α-anomer **5aα**, (–)-specionin was synthesized by sequences analogous to those outlined in Schemes 4 (**5aα** → **6aα** → **14α** → **15α** → **16α** → **17α**) and 6 (**17α** → **23α** → **24α** → **25α** → **27α** → **28α**). The most striking feature was found in the stereoselective introduction of 3-ethoxy group (Scheme 8). Benzoylation of **28α** provided the precursor **30α**. Upon ethoxymercuration of **30α** (EtOH, $Hg(OAc)_2$, 25 °C), a single intermediate mercury adduct was obtained. Demercuration with 0.5 M sodium borohydride in 3 M NaOH[42] at –78 °C provided the desired 3β-ethoxy compound **32α** as a single stereoisomer in 70% yield. No evidence for the formation of even trace amounts of the 1α, 3α isomer was obtained.

Scheme 8



28α **30α** **32α** **4**

If the rate-determining step in the oxymercuration is attack by the ethanol, β-attack should be favored since α-attack would develop dipole-dipole repulsions between the incoming C3 ethoxy group and the axial-like C1 ethoxy group. The β-C1 ethoxy isomer shows no stereoselectivity in the oxymercuration since its ethoxy group is equatorially disposed. Another possible explanation for the stereoselective formation of **30α** is based on the possibility that the oxymercuration is an equilibrium process.[38] The results for the two epimers parallel the specionin equilibrium: the β-C1 epimers are of comparable energy but one of the α-C1 epimers is of much lower energy than the other.

Only deprotection was now required. After desilylation of **32α** with tetra-*n*-butylammonium fluoride trihydrate in THF at room temperature, and palladium-catalyzed hydrogenolytic cleavage of the benzyl group, (–)-specionin (**4**) was isolated as a clear oil in 90% yield. Our synthetic specionin was identical in all respects (^1H NMR, ^{13}C NMR, IR, mass spectroscopy, analytical HPLC, TLC, optical rotation) with a sample kindly provided by Professor Nakanishi via Professor Vandewalle. The optical rotation of specionin had apparently not been recorded and we were able to measure that of both synthetic and natural samples (see Experimental). Recently, Professor Vandewalle has also prepared specionin from catalpol.[40] Thus, the absolute stereochemistry of specionin is as depicted.

In conclusion, this work should provide a general entry into a broad class of iridoid aglycones which lack the stabilizing C11 carbomethoxy group and contain a sensitive enol acetal. In addition to the synthesis of specionin, both anomers of ethyl catalpol and β-descarbomethoxy verbenalol were prepared. It is easy to envision that the advanced intermediates prepared in this work might be applicable to the synthesis of related iridoids with differing oxygenation requirements.[34] The coupling of iridoid aglycones and sugars remains a challenging problem which has seen some important recent advances.[43,44]

Experimental[45]

General: All reactions were run under a nitrogen atmosphere unless noted. Temperatures of reactions refer to bath temperatures. Solvents were dried as follows: THF, Et_2O, and benzene, distilled from Na/benzophenone; toluene, Et_3N, diisopropylamine, CH_2Cl_2, HMPA, diisopropylethylamine, DMF, DMSO, and DMPU distilled from CaH_2. Flash and medium pressure (MPLC) liquid chromatography were performed with Kieselgel 60 (230-400 mesh). Medium pressure chromatography was also done on pre-packed EM Lobar LiChroprep Si/60 columns. Thin layer chromatography was performed on Merck silica gel 60 pre-coated plates. All reported boiling and melting points are uncorrected. The temperatures

recorded during Kugelrohr distillations refer to oven temperatures. All NMR's were recorded at 300MHz (75MHz, ^{13}C) in $CDCl_3$ unless noted. Unless noted, IRs were recorded in $CHCl_3$ solution.

(2*R*-*trans*)-2-Ethoxy-3,6-dihydro-2*H*-pyran-3-acetic acid, methyl ester (6aβ).

n-Butyllithium (30.8 mL, 1.6 M in hexane, 49.5 mmol) was added dropwise via syringe to a stirred solution of diisopropylamine (7.3 mL, 52 mmol) in dry THF (50 mL) at 0°C. After stirring for 15 min, the resulting straw colored solution was cooled to –78°C and **5aβ**[14] (8.33 g, 45 mmol) in THF (8 mL) was added dropwise via syringe. After 3 min, *t*-butyldimethylchlorosilane (30 mL, 1.66 M soln, 49.5 mmol) in HMPA was added and the reaction was allowed to warm to 0°C for 35 min. This was poured into a cold mixture of water and pentane. After separation of the phases, the organic layer was washed with water (3x) and brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure to give the crude ketenesilyl acetal (13.5 g): ^1H NMR δ 0.20 (s, 6H), 0.95 (s, 9H), 1.24 (t, 3H), 3.23 (dd, 2H), 3.34- 4.24 (m, 4H), 4.92 (d, 2H), 5.75- 6.05 (m, 2H). The crude ketenesilyl acetal in dry toluene (20 mL) was heated at 80°C for 20 h. The reaction was cooled to room temperature and concentrated to give the rearranged silyl ester: ^1H NMR δ 0.03 (s, 6H), 0.95 (s, 9H), 1.24 (t, 3H), 2.50 (m, 3H), 3.60 (m, 2H), 3.90 (dd, 1H), 4.16 (d, 2H), 4.62 (d, 1H), 5.76 (s, 1H). To the crude silyl ester in HMPA (30 mL) was added KF (10.46 g, 180 mmol), $KHCO_3$ (18.0 g, 180 mmol), and water (3.2 mL, 180 mmol). The reaction mixture was stirred for 8 h at 25°C after which methyl iodide (22.4 mL, 360 mmol) was added. The mixture was stirred for 12 h before being poured into water and ether. The phases were separated and the aqueous layer was extracted with ether (2x). The combined organic layer was washed with water (3x) and brine (1x), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5% ethyl acetate/hexane) provided 5.95 g (66% yield) of the methyl ester **6a**, as a yellow oil: IR 2975, 1730, 1435, 1265, 1115, 1055 cm^{-1}; ^1H NMR δ 1.24 (t, 3H), 2.37 (dd, 1H, J = 15, 7 Hz), 2.52 (m, 1H), 2.61, (broad, 1H), 3.40 (dq, 1H), 3.70 (s, 3H), 3.87 (dq, 1H), 4.08 (dq, 1H, J = 16, 2.4 Hz), 4.22 (dq, 1H, J = 16, 2.4 Hz), 4.60 (d, 1H, J = 2.8 Hz), 5.69 (dm, 1H, J = 10.5 Hz), 5.78 (dm, 1H, J = 12 Hz); MS *m/e* 200 (M^+), 169, 155, 127, 126, 108, 84 (base); MS calcd for $C_9H_{13}O_3$ (M – OMe), 169.0865; found 169.0866.

(2*S*-*cis*)-2-Ethoxy-3,6-dihydro-2*H*-pyran-3-acetic acid, methyl ester (6aα).

IR (neat) 2977, 1738, 1167, 1123, 1059 cm^{-1}; ^1H NMR δ 5.76-5.72 (m, 1H), 5.62-5.57 (m, 1H), 4.85 (d, 1H, J = 3.8 Hz), 4.17-4.09 (m, 2H), 3.85-3.79 (m, 1H), 3.67 (s, 3H), 3.52-3.47 (m, 1H), 2.88 (m, 1H), 2.58 (dd, 1H, J = 15.4, 7.9 Hz), 2.30 (dd, 1H, J = 15.4, 7.9 Hz), 1.18 (t, 3H, J = 6.6 Hz); MS *m/e* 200 (M^+), 169, 155, 126, 84 (base), 67; MS calcd for $C_{10}H_{16}O_4$, 200.1048; found, 200.1036; MS calcd for $C_9H_{13}O_3$ (M – OCH_3), 169.0865; found, 169.0871.
$[\alpha]_D^{25}$ = + 70.4° (c = 0.725, $CHCl_3$).

{2*R*-[2α,3ß(*S)]}-2-Ethoxy-3,6-dihydro-3-(1'-thiophenyl)-2*H*-pyran-3-acetic acid, methyl ester (13β).**

Lithium diisopropylamide (LDA) was generated as above using *n*-butyllithium (7.1 mL, 1.6 M soln, 11 mmol) and diisopropylamine (1.7 mL, 12 mmol) in THF (15.2 mL). The ester **5β** (1.99 g, 10 mmol) in THF (15 mL) was added dropwise via syringe to the LDA at –78°C and the reaction was stirred for 1 h. The reaction was allowed to warm to –25°C and diphenyl disulfide (2.4 g, 11 mmol) in THF (10 mL) was added dropwise via syringe. The reaction mixture was allowed to warm to 25°C and was stirred for 1.5 h before being poured into water and ethyl acetate. The phases were separated and the aqueous layer was extracted with ethyl acetate (2x). The combined organic phases were washed with saturated $NaHSO_4$ (1x), water (1x), saturated $NaHCO_3$ (1x), water (2x), and brine (1x). The resulting solution was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude α–sulfenyl ester **13β**. Purification by flash chromatography (16% ethyl acetate/hexane) gave pure **13β** (2.345 g, 76% yield). The ratio of diastereomers as determined by ^1H NMR analysis was about 1:1.

{2*S*-[2α,3α(*R)]}-2-Ethoxy-3,6-dihydro-3-(1'-thiophenyl)-2*H*-pyran-3-acetic acid, methyl ester (13α).**

IR (neat) 2994, 1740, 1252, 1150, 1073 cm^{-1}; ^1H NMR δ 7.51-7.26 (m, 5H), 6.18-6.15, 5.90-5.86, 5.82-5.77, 5.47-5.42 (m, 2H), 5.24, 4.90 (both d, 1H, J = 4.3, 3.8 Hz), 4.21-3.97 (m, 3H), 3.86-3.71, 3.52-3.37 (both m, 2H), 3.77, 3.52 (both d, 1H, J = 3.8, 3.5 Hz), 3.67, 3.66 (both s, 3H), 2.98-2.91, 2.82-2.77 (both m, 1H), 1.12 (t, 3H, J = 6.2 Hz); MS *m/e* 308 (M^+), 153, 84, 49 (base); MS calcd for $C_{16}H_{20}O_4S$, 308.1082; found, 308.1044.

{2*R*-[2α,3ß(S*)]}-2-Ethoxy-3,6-dihydro-3-(1'-thiophenyl-1'-carbomethoxy)-3-nitropropyl)-2*H*-pyran (14β).

LDA was generated (*n*-butyllithium, 5.42 mL, 8.4 mmol; diisopropylamine, 1.3 mL, 9.1 mmol; THF, 10 mL) and cooled to -78°C. The sulfide **13β** (2.35 g, 7.6 mmol) in THF (19 mL) was added dropwise and after 30 min, freshly distilled nitroethylene[24] (12 mL, 1M in benzene, 12 mmol) was also added dropwise. The resulting solution was stirred for 1 h, then warmed to 25°C and stirred for 30 min. This was poured into saturated NH_4Cl and ether, the organic layer was separated, and the aqueous layer was extracted with ether (2x). The combined organic phases were washed with water (1x), saturated $NaHCO_3$ (1x) and water (1x), and dried over $MgSO_4$. The resulting solution was filtered and concentrated to yield 2.62 g (90%) of the nitro compound **14β** as a mixture of diastereomers: IR 2970, 2920, 2850, 1725, 1550, 1435, 1380 cm^{-1}; ^1H NMR δ 1.21 (t), 1.30 (t), 3.58 (s) and 3.69 (s) in a ratio of 1.8:1, 5.49 (s), 6.07 (s).

{2*S*-[2α,3α(*R)]}-2-Ethoxy-3,6-dihydro-3-(1'-thiophenyl-1'-carbomethoxy-3-nitropropyl)-2*H*-pyran (14α).**

IR (neat): 2994, 1735, 1570, 1447, 1223, 1073 cm^{-1}; ^1H NMR δ 7.50-7.31 (m, 5H), 6.13, 6.00, 5.81 (m, 2H), 5.22, 4.80 (both d, 1H), 5.01-4.88, 4.66-4.54 (both m, 2H), 4.30-4.00 (m, 2H), 3.91-3.31 (m, 5H), 3.21, 3.04 (both m, 1H), 2.90-2.42 (m, 2H), 1.25, 1.14 (both t, 3H, J = 6.6 Hz); MS *m/e* 381(M^+), 307, 272, 207, 198, 91, 81 (base), 69; MS calcd for $C_{18}H_{23}NO_6S$, 381.1246; found, 381.1246.

[4*S*-(4α,4aα,5α,7aα,7bα)]-5-Ethoxy-3,4,4a,7,7a,7b-hexahydro-4-carbomethoxy-4-thiophenyl-5*H*-1,6-dioxa-2-azacyclopent(cd)indene (15β).

A mixture of the nitro compound **14β** (2.44 g, 6.4 mmol), triethylamine (1.5 mL, 10.8 mmol), and methyl isocyanate (1.5 mL, 25.6 mmol) in benzene (55 mL) was stirred for 14 h at 25°C, then heated in a pressure bottle at 85°C with stirring for 1 h. The reaction was cooled to 25°C, and water (40 mL) was added and the mixture stirred for 2 h. The organic layer was separated and concentrated. The organic residue was dissolved in EtOAc, washed with H_2O (3x) and brine (1x), dried over $MgSO_4$, filtered, and concentrated. The resulting yellow oil was dissolved in EtOAc, filtered through Florisil, and concentrated to yield 2.32 g (100%) of crude isoxazoline. For purposes of identification, the diastereomers were separated by flash chromatography (25% EtOAc/hexane): diastereomer I (R_f = 0.58 in 45% EtOAc in hexane); mp 158-9°C; IR 3100, 3000, 2970, 2920, 1715 (weak) cm^{-1}; ^1H NMR δ 1.30 (t, 3H), 2.68 (dd, 1H, J = 19, 1 Hz), 2.90 (t, 1H, J = 6 Hz), 3.51 (dt, 1H, J = 19, 1Hz), 3.58 (s, 3H), 3.60 (dd, 1H, J = 11, 3 Hz), 3.69 (dq, 1H), 3.82 (dd, 1H, J = 15, 4 Hz), 3.86 (dq, 1H), 4.64 (dt, 1H, J = 8, 3 Hz), 5.04 (d, 1H, J = 4 Hz), 7.37 (m 3H), 7.54 (m, 2H); diastereomer II (R_f = 0.63 in 45% EtOAc in hexane); ^1H NMR δ 1.17 (t, 3H), 2.40 (t, 1H, J = 6 Hz), 2.76 (dt, 1H, J = 19, 1 Hz), 3.20 (dd, 1H, J = 19, 2 Hz), 3.37 (dq, 1H), 3.53 (dd, 1H, J = 13, 6 Hz), 3.70 (dq, 1H), 3.79 (s, 3H), 3.88 (dd, 1 H, J = 13 Hz, J = 6 Hz), 4.32 (d, 1H, J = 6 Hz), 4.72 (m, 1H), 7.36-7.48 (m, 5H); MS *m/e* 363 (M^+, base), 334, 320, 303, 289, 258, 254, 224, 208, 194, 180, 169, 148, 135, 120, 110; MS calcd for $C_{18}H_{21}NO_5S$, 363.1140; found, 363.1142; Analysis calcd for $C_{18}H_{21}NO_5S$: C, 59.65%; H, 5.82%. Found: C, 59.66%; H, 5.90%.

[4*S*-(4α,4aα,5β,7aα,7bα)]-5-Ethoxy-3,4,4a,7,7a,7b-hexahydro-4-carbomethoxy-5*H*-1,6-dioxa-2-azacyclopent(cd)indene (15α).

Mixture of diastereomers: IR (neat) 2967, 1730, 1250, 1050, 1025 cm^{-1}; ^1H NMR δ 7.46-7.29 (m, 5H), 5.18, 4.90 (both d, 1H, J = 5.4, 5.81 Hz), 4.83, 4.73 (both dd, 1H), 3.74, 3.34 (both s, 3H), 3.77-3.50, 3.30-3.05 (m, 7H), 2.70-2.57 (m, 1H), 1.31, 1.06 (both t, 3H); MS *m/e* 363 (M^+), 317, 289, 254, 208, 180, 120(base), 109; MS calcd for $C_{18}H_{12}NO_5S$, 363.1141; found, 363.1133.

[4*S*-(4α,4aα,5α,7aα,7bα)]-5-Ethoxy-4a,7,7a,7b-tetrahydro-4-carbomethoxy-5*H*-1,6-dioxa-2-azacyclopent(cd)indene (16β).

To a diastereomeric mixture of **15β** (5.48 g, 15.1 mmol) in methylene chloride (75 mL) and saturated $NaHCO_3$ (75 mL) at 0°C was added *m*-chloroperoxybenzoic acid (3.1 g, 15.1 mmol) in CH_2Cl_2 (75 mL). The reaction mixture was stirred for 1 h at 0°C, then allowed to warm to 25°C. The mixture was poured into CH_2Cl_2 and saturated $NaHSO_3$, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic phases were washed with H_2O (1x), saturated $NaHCO_3$ (1x), H_2O (3x), and brine (1x), dried over Na_2SO_4, and concentrated. The resulting oil was dissolved in benzene (70 mL) and heated at 85°C for 5 h. The brown oil obtained by removal of benzene at reduced pressure was purified by flash chromatography (27% EtOAc/hexane) to yield 3.05 g (80%) of **16β** as yellow oil: IR 3000, 2910, 2850, 1715 cm^{-1}; ^1H NMR δ 1.24 (t, 3H), 3.06 (d, 1H, J = 13 Hz), 3.47 (dq, 1H), 3.64 (dq, 1H), 3.71 (d, 1H, J = 14 Hz), 3.86 (s, 3H), 3.90 (dd, 1H, J = 14, 5 Hz), 4.12 (dd, 1H, J = 10, 8 Hz), 6.73 (s, 1H), 6.75 (dd, 1H, J = 11, 4 Hz), 7.26 (s, 1H); MS *m/e* 253 (M^+, base), 226, 179, 120, 119, 117; MS calcd for $C_{12}H_{15}NO_5$, 253.0950; found, 253.0951.

[4*S*-(4α,4aα,5β,7aα,7bα)]-5-Ethoxy-4a,7,7a,7b-tetrahydro-4-carbomethoxy-5*H*-1,6-dioxa-2-azacyclopent(cd)indene (16α).

IR (neat) 2961, 1734, 1250, 1090, 1040 cm^{-1}; ^1H NMR δ 7.11 (br s, 1H), 4.94 (d, 1H, J = 6.7 Hz), 4.86 (dd, 1H, J = 14.1, 6.6 Hz), 4.06 (m, 1H), 3.81 (s, 3H), 3.81-3.29 (m, 5H), 1.07 (t, 3H, J = 5.7 Hz); MS *m/e* 253(M^+), 208, 179, 120 (base), 92, 59; MS calcd for $C_{12}H_{15}NO_5$, 253.0950; found, 253.0951; Analysis calcd for $C_{12}H_{15}NO_5$: C, 56.91%; H, 5.97%; found C, 57.21%, H, 5.83%; $[\alpha]_D^{25} = -73.8°$ (c = 0.785, $CHCl_3$).

[4*S*-(4α,4aα,5α,7aα,7bα)]-5-Ethoxy-4a,7,7a,7b-tetrahydro-4-hydroxymethyl-5*H*-1,6-dioxa-2-azacyclopent(cd)indene.

n-Butyllithium (14.5 mL, 1.55M, 22.7 mmol) was added dropwise via syringe to a solution of DIBAL (23.0 mL, 1M, 22.7 mmol) at -78°C, resulting in a gelatinous precipitate which dissolved upon dropwise addition of THF (8 mL). At -78°C the clear aluminate solution was added via syringe to **16β** (2.83 g, 11.2 mmol) in THF (24 mL) and the mixture was stirred for 1 h before warming to 0°C for 5 min. Citric acid (11 mL, 0.5 M solution) and MeOH (0.5 mL) were added quickly and the mixture was stirred at 25°C for 1 h. The reaction mixture was salted with NaCl and extracted with ethyl acetate (5x). The phases were separated and the combined organic layers were washed with brine (3x), dried over $MgSO_4$, and concentrated to yield 2.32 g of a pale yellow oil (92% yield): IR 3400 (broad), 2970, 2920, 1710 (weak) cm^{-1}; ^1H NMR δ 1.24 (t, 3H), 2.86 (dd, 1H, J = 6, 7 Hz), 3.42 (dd, 1H, J = 12, 6.5 Hz), 3.50 (dq, 1H), 3.84 (dq, 1H), 4.01 (dd, 1H, J = 12, 7 Hz), 4.13 (t, 1H, J = 7 Hz), 4.34 (d, 1H, J = 6 Hz), 4.40 (s, 2H), 4.76 (m, 1H), 6.43 (s, 1H); MS *m/e* 225 (M^+), 179, 151, 133, 117, 68 (base); MS calcd for $C_{11}H_{15}NO_4$, 225.1001; found, 225.1001.

[4*S*-(4α,4aα,5β,7aα,7bα)]-5-Ethoxy-4a,7,7a,7b-tetrahydro-4-hydroxymethyl-5*H*-1,6-dioxa-2-azacyclopent(cd)indene.

IR (neat) 3382 (broad), 2957, 1109, 1050 cm^{-1}; ^1H NMR δ 6.42 (br s, 1H), 4.76 (d, 1H, J = 5.9 Hz), 4.65 (dt, 1H, J = 9, 5.5 Hz), 4.40 (s, 2H), 4.08-3.88 (m, 2H), 3.79 (dq, 1H), 3.55 (dd, 1H, J = 12.3, 5.5 Hz), 3.44 (m, 1H), 3.22 (br t, 1H, J = 7 Hz), 1.20 (t, 3H, J = 6.2 Hz).

[4*S*-(4α,4aα,5α,7aα,7bα)]-5-Ethoxy-4a,7,7a,7b-tetrahydro-4-[(*t*-butyldimethylsilyl)oxy]methyl-5*H*-1,6-dioxa-2-azacyclopent(cd)indene (17β).

A mixture of crude alcohol described above (238 mg, 1.05 mmol), *t*-butyldimethylsilyl chloride (TBSCl) (238mg, 1.6 mmol), and imidazole (176 mg, 2.6 mmol) in dimethylformamide (5.3 mL) was stirred for 16 h at 45°C. The reaction mixture

was then poured into ether and saturated $NaHSO_4$, the layers were separated, and the aqueous layer was extracted with ether (2x). The combined organic phases were washed with water (1x), saturated $NaHCO_3$ (1x), water (3x) and brine (1x), filtered through Florisil, dried over $MgSO_4$, and concentrated: IR 2920, 2850 cm^{-1}; ^1H NMR δ 0.10 (s, 6H), 0.92 (s, 9H), 1.22 (t, 3H), 2.76 (dd, 1H, J = 7, 6 Hz), 3.37-3.52 (m, 2H), 3.81 (dq, 1H), 3.98 (dd, 1H, J = 13, 7 Hz), 4.11 (t, 1H, J = 9, 6 Hz), 4.33 (d, 1H, J = 6 Hz), 4.37 (d, 2H, J = 1 Hz), 4.72 (dt, 1H, J = 11, 6 Hz), 6.43 (s, 1H); MS *m/e* 339 (M^+), 293 (base), 282, 264, 238, 208; $[\alpha]_D^{25} = -90.0°$ (c = 1.0, $CHCl_3$).

[4*S*-(4α,4aα,5β,7aα,7bα)]-5-Ethoxy-4a,7,7a,7b-tetrahydro-4-[(*t*-butyldimethylsilyl)oxy]methyl-5*H*-1,6-dioxa-2-oxacyclopent(cd)indene (17α).

mp 110-111 °C; IR (neat): 2957, 1550, 1080, 835 cm^{-1}; ^1H NMR δ 6.38 (br s, 1H), 4.72 (d, 1H, J = 6.2 Hz), 4.63 (m, 1H), 4.48 (dd, 1H, J = 16.4, 1.6 Hz), 4.27 (dd, 1H, J = 16.4, 0.9 Hz), 4.00 (t, 1H, J = 8.7 Hz), 3.91 (dd, 1H, J = 11.9, 6.2 Hz), 3.74 (m, 1H), 3.52 (dd, 1H, J = 11.9, 6.2 Hz), 3.36 (m, 1H), 3.11 (t, 1H, 7.0 Hz), 1.16 (t, 3H, 7.0 Hz), 0.93 (s, 9H), 0.09 (s, 6H); MS *m/e* 339 (M^+), 324, 293, 117, 75 (base); MS calcd for $C_{17}H_{29}NO_4Si$, 339.1866; found, 339.1866; $[\alpha]_D^{25} = -31.6°$ (c = 1.64, $CHCl_3$).

[4S-(3α,4aα,5α,7aα,7bα)]-5-Ethoxy-3,4a,7,7a,7b-pentahydro-4ß-[(*t*-butyldimethylsilyl)oxy]methyl-3,4-oxireno-1,6-dioxa-2-oxacyclopent(cd)indene (23β).

A mixture of the unsaturated isoxazoline **17β** (300 mg, 0.89 mmol), 3,5-dinitroperoxybenzoic acid (540 mg, ~70% active, 1.77 mmol), 4,4'-thiobis(2-*t*-butyl-6-methylphenol) (5 mg, 0.014 mmol), and NaH_2PO_4 (1.0 g, 7.08 mmol) in methylene chloride (6.0 mL) was stirred for 5 h at 25°C. The reaction mixture was poured into saturated aqueous $NaHSO_3$ and the phases were separated. The aqueous layer was extracted with methylene chloride (3x) and the combined organic phases were washed with water (1x), $NaHCO_3$ (1x), water (3x), and brine (1x). After drying over Na_2SO_4, the reaction was concentrated to provide 321 mg of the crude product: IR 2923, 2850, 1710 (weak), 1460, 1375, 1100, 835 cm^{-1}; ^1H NMR δ 0.08 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 1.22 (t, 3H), 2.54 (dd, 1H, J = 5.3, 8.6 Hz), 3.36 (dd, 1H, J = 5.5, 12.9 Hz), 3.50 (dq, 1H), 3.73-3.86 (m, 2H), 3.91 (d, 1H, J = 12.6 Hz), 3.91 (dd, 1H, J = 6.0, 12.8 Hz), 4.01 (s, 1H), 4.16 (d, 1H, J = 12.6 Hz), 4.59 (d, 1H, J = 5.3 Hz), 4.73 (m, 1H); *MS m/e* (no M^+) 310, 298, 252, 244 (base), 206, 194, 182, 169; MS calcd for $C_{13}H_{20}NO_5Si$ (M – *t*-Bu), 298.1111; found, 298.1111; $[\alpha]_D^{25} = -63.6°$ (c = 2.0, $CHCl_3$).

[4*S*-(3α,4aα,5β,7aα,7bα)]-5-Ethoxy-3,4a,7,7a,7b-penyahydro-4β-[(*t*-butyldimethylsilyl)oxy]methyl-3,4-oxireno-1,6-dioxa-2-azacyclopent(cd)indene (23α).

IR (neat) 2953, 1157, 1115, 1063, 831 cm^{-1}; ^1H NMR δ 5.03 (d, 1H, J = 6.0 Hz), 4.83 (m, 1H), 4.38 (d, 1H, J = 6.0 Hz), 3.87 (br s, 1H), 3.66 (d, 1H, J = 6.0 Hz), 3.66-3.36 (m, 5H), 2.88 (dd, 1H, J = 9.2, 5.7 Hz), 1.19 (t, 3H, J = 7.0 Hz), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); MS *m/e* 310, 298, 252, 145, 75 (base); MS calcd for $C_{13}H_{20}NO_5Si$ (M – *t*-Bu), 298.1111; found, 298.1111.

[1*R*-(1α,4ß,4aα,6α,7aα)]-1-Ethoxy-3,4,4a,6,7a-pentahydro-4-hydroxy-7ß-[(*t*-butyldimethylsilyl)-oxy]methyl-6,7-oxireno-cyclopenta(c)pyran-5-(1*H*)-one (24β).

A solution of the epoxyisoxazoline **23β** (129 mg, 0.36 mmol) and boric acid (67 mg, 1.08 mmol) in methanol/water (5:1, 1.5mL) was stirred with rhodium (5% on alumina, spatula tip) under hydrogen atmosphere at 25°C for 1.5 h. The reaction mixture was filtered through Florisil with methanol and concentrated. The residue was then dissolved in ether and again filtered through Florisil with ether and concentrated. The crude product **24β** (95 mg) was recovered as a pale yellow oil (74% crude yield): IR 3500 (broad), 2930, 2855, 1735 cm^{-1}; ^1H NMR δ 0.07 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.23 (t, 3H), 2.85 (dd, 1H, J = 4.8, 7.8 Hz), 3.06 (t, 1H, J = 7 Hz), 3.29 (t, 1H, J = 10.5 Hz), 3.39, (s, 1H). 3.50 (dq, 1H), 3.85 (dq, 1H,), 3.89 (d, 1H, J = 12.7 Hz), 3.94 (dd, 1H, J = 6.4, 11.0 Hz), 4.17 (m, 1H), 4.19 (d, 1H, J = 12.7 Hz), 4.53 (d, 1H, J = 4.8 Hz); ^1H NMR (C_6D_6) δ –0.09 (s, 3H), 0.01 (s, 3H), 0.90 (s, 9H), 0.98 (t, 3H), 2.65 (dd, 1H, J = 4.6, 7.7 Hz), 2.76 (t, 1H, J = 7Hz), 3.06 (s, 1H), 3.12 (dq, 1H), 3.23 (t, 1H, J = 10 Hz), 3.52 (d, 1H, J = 12.7 Hz), 3.58 (dq, 1H), 3.84 (dd, 1H, J = 6.2, 10.8 Hz), 3.85 (m, 1H), 3.90 (d, 1H, J = 12.6 Hz), 4.11 (m, 1H), 4.25 (d, 1H, J = 4.7 Hz); MS *m/e* (no M^+) 301, 285, 283, 255 (base), 237, 227, 209, 181; MS calcd for $C_{13}H_{19}O_5Si$ (M – *t*-Bu and H_2O), 283.1002; found, 283.0095; $[\alpha]_D^{25}$ (crude) = –16.3° (c = 1.0, $CHCl_3$).

[1*S*-(1β,4β,4aα,6α,7aα)]-1-Ethoxy-3,4,4a,6,7a-pentahydro-4-hydroxy-7β-[(*t*-butyldimethylsilyl)oxy]-methyl-6,7-oxirenocyclopenta(c)pyran-5-(1*H*)-one (24α).

IR (neat): 3432, 2953, 1734, 1246, 1069, 1011, 853 cm^{-1}; ^1H NMR δ 4.93 (d, 1H, J = 2.1 Hz), 4.24 (d, 1H, J = 12.0 Hz), 4.05 (d, 1H, J = 11.1 Hz), 3.93-3.89 (m, 1H), 3.64 (d, 1H, J = 12.0 Hz), 3.71-3.57 (m, 2H), 3.50-3.35 (m, 2H), 3.24 (br s, 1H), 3.04-3.02 (m, 2H), 1.16 (t, 3H, J = 6.6 Hz), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); MS *m/e* (no M^+) 301, 255, 175, 99 (base), 75; MS calcd for $C_{13}H_{21}O_6Si$ (M – t-Bu), 301.1107; found, 301.1106; $[\alpha]_D^{25}$ = + 121.8° (c = 0.85, $CHCl_3$).

[1*R*-(1α,6α,7aα)]-1-Ethoxy-3,6,7a-trihydro-7ß-[(*t*-butyldimethylsilyl)oxy]methyl-6,7-oxireno-cyclopenta(c)pyran-5(1*H*)-one (25β).

Methanesulfonyl chloride (10.5 µL, 0.14 mmol) was added to the epoxy ß-hydroxy ketone **24β** (30 mg, 0.084 mmol) and triethylamine (0.050 mL, 0.36 mmol) in methylene chloride (1.0 mL) and the reaction was stirred at 25°C for 30 min. The reaction was washed with $NaHSO_4$ (1x) and extracted with methylene chloride (3x). The combined organic phases were washed with $NaHCO_3$ (1x), water (2x), and brine (1x), then dried over Na_2SO_4 and concentrated. The crude product (35 mg) was obtained in almost quantitative yield; IR 2950, 2925, 2875, 2850, 1725 (strong), 1650, 1460, 1435, 1380, 1350, 1200, 1155, 1100, 1040, 1010, 835 cm^{-1}; ^1H NMR δ 0.06 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.27 (t, 3H), 3.01 (m, 1H), 3.57 (dq, 1H), 3.59 (s, 1H), 3.98 (dq, 1H), 4.01 (d, 1H, J = 12.5 Hz), 4.16 (d, 1H, J = 12.5 Hz), 4.39 (d, 1H, J =

7.4 Hz), 4.44 (t, 1H, J = 3.2 Hz), 4.65 (dt, 1H, J = 4.8, 19.5 Hz), 6.62 (dd, 1H, J = 4.8, 2.3 Hz); MS *m/e* (no M^+), 253, 237, 209, 179, 153, 153, 135, 107; $[\alpha]_D^{25}$ (crude) = +0.64 (c = 1.1, $CHCl_3$).

[1*S*-(1β,6α,7aα)]-1-Ethoxy-3,6,7a-trihydro-7β-[(*t*-butyldimethylsilyl)oxy]methyl-6,7-oxireno-cyclopenta(c)pyran-5(1*H*)-one (25α).

IR (neat) 2930, 1732, 1653, 1096, 837 cm^{-1}; ^1H NMR δ 6.69-6.67 (m, 1H), 5.37 (d, 1H, J = 3.7 Hz), 4.17 (dt, 2H), 4.41, 3.60 (both d, 2H, J = 12.0 Hz), 3.78-3.55 (m, 2H), 3.44 (d, 1H, J = 1.4 Hz), 3.16-3.14 (m, 1H), 1.18 (t, 3H, J = 7.0 Hz), 0.92 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); MS *m/e* 283, 237, 209, 75 (base); MS calcd for $C_{13}H_{19}O_5Si$ (M – *t*-Bu), 283.1002; found, 283.1002; $[\alpha]_D^{25}$ = + 98.8° (c = 0.57, $CHCl_3$).

[1*R*-(1α,5α,6α,7aα)]-1-Ethoxy-3,5,6,7a-tetrahydro-5-hydroxy-7ß-*t*-butyldimethylsilyloxymethyl-6,7-oxirenocyclopenta(c)pyran (27β).

To LAH (5 mg, 0.13 mmol) at –78°C was added dropwise via syringe a solution of **25β** (22mg, 0.065 mmol) in ether (1.5 mL). After the addition was finished, the reaction was quenched by sequential addition of water (5 μL), 15% aqueous NaOH (5 μL), and water (15 μL), and the mixture was warmed to 25°C. The mixture was then filtered through Florisil, eluted with ethyl acetate, and concentrated. The product was purified by MPLC (45% ethyl acetate/hexane) to yield 9 mg of **27β** (41%), and 3 mg (14%) of **26β**. The data are for **27β**: IR 3571, 2955, 2930, 2856, 1742 (weak), 1472, 1462, 1391, 1377, 1350, 1285, 1254, 1179, 1154, 1100, 1067, 1046, 1030, 1019, 967, 940, 909 cm^{-1}; ^1H NMR δ 0.047 (s, 3H), 0.058 (s, 3H), 0.88 (s, 9H), 1.26 (t, 3H), 2.33 (d, 1H, J = 11.1 Hz), 2.83 (m, 1H), 3.52 (dq, 1H), 3.79 (d, 1H, J = 2.5 Hz), 3.98 (dq, 1H), 3.90 (d, 1H, J = 12.6 Hz), 4.01 (d, 1H, J = 12.7 Hz), 4.21 (dt, 1H, J = 3.0, 17.0 Hz), 4.31 (d, 1H, J = 8.1 Hz), 4.42 (br d, 1H, J = 17.0 Hz), 4.53 (br d, 1H, J = 10.5 Hz), 5.77 (d, 1H, J = 2.6 Hz); MS *m/e* (no M^+), 285, 267, 251, 239, 211, 193, 181, 165; MS calcd for $C_{13}H_{21}O_5Si$ (M – *t*-Bu), 285.1158; found, 285.1157; $[\alpha]_D^{25}$ = –66.6° (c = 0.95, $CHCl_3$).

[1*S*-(1β,5α,β,6α,7aα)]-1-ethoxy-3,5,6,7a-tetrahydro-5-hydroxy-7β-(*t*-butyldimethylsilyl)oxymethyl-6,7-oxireno-cyclopenta(c)pyran (26α and 27α).

The diastereomers were not separable at this step: IR (neat) 3428, 2955, 1462, 1090, 837 cm^{-1}; ^1H NMR δ 5.90, 5.85* (both m, 1H), 5.33, 5.30* (both d, 1H, J = 4.1 Hz), 4.60*, 4.48 (both br d, 1H), 4.37 (d, 1H, J = 11 Hz), 4.29-4.01 (m, 2H), 3.84-3.54 (m, 2H), 3.51 (d, 1H, J = 11Hz), 3.63*, 3.38 (both d, 1H, J = 1.4 Hz), 3.02*, 2.84 (both m, 1H), 2.28*, 2.05 (both d, 1H), 1.20 (t, 3H, J = 7.0 Hz), 0.91 (s, 9H), 0.1 (s, 3H), 0.08 (s, 3H). *Represents peak of the major product.

10-*O*-*t*-Butyldimethylsilyl catalpol, β-ethyl acetal (28β).

Alcohol **27β** (4 mg, 0.01 mmol) in ethanol (1.0 mL) was added to dihydridotris(triphenylphosphine) ruthenium (II) (4 mg, 0.0035 mmol) under argon atmosphere. The reaction mixture was heated at reflux (90°C) for 5 h, then filtered through Florisil with ethyl acetate and concentrated. The product obtained was purified by MPLC (25% ethyl acetate/hexane) yielding 3.6 mg of **28β** (90%): IR (CCl_4) 3592, 3450 (broad), 2955, 2930, 2884, 2857, 1653, 1472, 1462, 1379, 1362, 1256, 1225, 1215, 1148, 1115, 1176, 1053, 1030, 990, 962 cm^{-1}; ^1H NMR δ 0.03 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.26 (t, 3H), 1.78 (d, 1H, J = 10.0 Hz), 2.25-2.31 (m, 1H), 2.48 (dd, 1H, J = 8, 9 Hz), 3.54 (d, 1H, J = 1.0 Hz), 3.57 (dq, 1H), 3.88 (br t, 1H, J = 8 Hz), 4.0 (dq, 1H), 4.02 (s, 1H), 4.43 (d, 1H, J = 9 Hz), 5.04 (dd, 1H, J = 4.5, 6.0 Hz), 6.32 (dd, 1H, J = 1.9, 6.0 Hz); MS *m/e* 342 (M^+), 285, 267, 239, 225, 211; MS calcd for $C_{13}H_{21}O_5Si$ (M – *t*-Bu), 285.1158; found, 285.1151; $[\alpha]_D^{25}$ = –67.50 (c = 0.36, $CHCl_3$).

10-*O*-*t*-Butyldimethylsilyl catalpol, α-ethyl acetal (28α).

The diasteromeric alcohols were readily separated at this stage: **28α**; mp 96-97 °C; IR (neat) 3270, 2857,1651, 1102, 1007, 839 cm^{-1}; ^1H NMR δ 6.18 (dd, 1H, J = 6.2, 1.8 Hz), 5.17-5.13 (m, 2H), 4.20-4.13 (m, 1H), 4.15 (d, 1H, J = 12.0 Hz), 3.78-3.72 (m, 1H), 3.57 (d, 1H, J = 12.1 Hz), 3.50-3.44 (m, 1H), 3.36 (d, 1H, J = 1.3 Hz), 2.81 (dd, 1H, J = 8.2, 3.4 Hz), 2.06-2.04 (m, 1H), 1.61 (d, 1H, J = 10.3 Hz), 1.17 (t, 3H, J = 7.1 Hz), 0.92 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); MS *m/e* 285, 267, 239, 81, 76 (base); MS calcd for $C_{13}H_{21}O_5Si$ (M – *t*-Bu), 285.1158; found, 285.1157.

Catalpol, β-ethyl acetal (29β).

An excess of tetrabutylammonium fluoride was added to silylated ethyl catalpol **28β** (4 mg, 0.01 mmol) in THF (0.5 mL). The reaction was stirred for 4 h at 25°C, then poured into hexane and water. The hexane layer was separated and the aqueous layer was extracted with ethyl acetate (5x). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The crude ethyl catalpol (2.5 mg) was recovered in nearly quantitative yield: IR (neat): 3507, 3347, 2924, 2853, 1713, 1651, 1456, 1377, 1345, 1262, 1223, 1140, 1119, 1088, 1055, 1017, 980, 956, 905, 770 cm^{-1}; ^1H NMR δ 1.30 (t, 3H), 2.26 (m, 1H), 2.61 (dd, 1H, J = 7.9, 9.3 Hz), 3.49 (s, 1H), 3.62 (dq, 1H), 3.67 (d, 1H, J = 13.5 Hz), 3.90 (d, 1H, J = 7.0 Hz), 4.07 (dq, 1H), 4.08 (d, 1H, J = 13.5 Hz), 4.42 (d, 1H, J = 9.67 Hz), 5.07 (dd, 1H, J = 4.5, 5.9 Hz), 6.33 (dd, 1H, J = 1.8, 5.9 Hz); MS *m/e* 228 (M^+), 209, 195, 182, 177, 169, 162, 151, 131, 123, 111, 95, 85; MS calcd for $C_{11}H_{16}O_5$, 228.0997; found, 228.0996.

6-*O*-Benzyl-10-*O*-*t*-butyldimethylsilyl catalposide, β ethyl acetal (30β).

Silylated ethyl catalpol **28β** (2 mg, 0.006 mmol) in methylene chloride was added to a mixture of p-benzyloxybenzoic acid (3 mg, 0.013 mmol), DMAP (catalytic amount), and dicyclohexylcarbodiimide (DCC) (2.5 mg, 0.012 mmol) and the reaction was stirred under argon atmosphere for 3 days. A few drops of water were added and the mixture was stirred for 4 h, then diluted with methylene chloride. The mixture was washed with saturated aqueous NH_4Cl (1x), saturated aqueous $NaHCO_3$ (1x), water (3x), and brine (1x), and dried over Na_2SO_4. The resulting residue was repeatedly dissolved in ether and filtered through Celite to remove excess urea. Purification by MPLC (10% ethyl acetate/hexane) afforded 3.4 mg of the crystalline benzoate; mp = 96-96.5°C; IR (neat) 3400 (broad), 2928, 2857, 1713, 1651, 1607, 1511, 1455, 1252, 1169,

1151, 1107, 1063, 1015, 845, 735 cm^{-1}; ^1H NMR δ 0.06 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.29 (t, 3H), 2.55 (dd, 1H, J = 7.9, 9.4 Hz), 2.70 (m, 1H), 3.61 (dq, 1H), 3.77 (s, 1H), 4.03 (dq, 1H), 4.05 (s, 2H), 4.53 (d, 1H, J = 9.5 Hz), 4.94 (dd, 1H, J = 4.6, 5.9 Hz), 5.08 (dd, 1H, J = 0.9, 8.1 Hz), 5.13 (s, 2H), 6.33 (dd, 1H, J = 1.7, 6.0 Hz), 7.00 (d, 2H, J = 8.9 Hz), 7.24-7.44 (m, 5H), 8.05 (d, 2H, J = 8.9 Hz); MS *m/e* (no M^+), 495, 477, 449, 395, 324, 309, 294, 267, 211, 91 (base); MS calcd for $C_{27}H_{31}O_7Si$ (M – *t*-Bu), 495.1839; found, 495.1810; $[\alpha]_D^{25} = -115.0°$ (c = 0.4, $CHCl_3$)

6-*O*-Benzyl-10-*O*-*t*-butyldimethylsilyl catalposide, α-ethyl acetal (30α).

IR (neat) 2928, 1715, 1605, 1254, 1102, 1051 cm^{-1}; ^1H NMR δ 8.04 (d, 2H, J = 8.7 Hz), 7.46-7.35 (m, 5H), 7.00 (d, 2H, J = 8.7 Hz), 6.20 (dd, 1H, J = 6.2, 1.5 Hz), 5.33 (d, 1H, J = 8.1 Hz), 5.23 (d, 1H, J = 3.3 Hz), 5.14 (s, 2H), 5.06 (t, 1H, J = 5.1 Hz), 4.22 (d, 1H, J = 12.1 Hz), 3.80 (m, 1H), 3.63 (s, 1H), 3.58 (d, 1H, J = 12.4 Hz), 3.55 (m, 1H), 2.89 (dd, 1H, J = 8.3, 3.3 Hz), 2.50 (m, 1H), 1.22 (t, 3H, J = 7.1 Hz), 0.92 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); MS *m/e* 552 (M^+), 495, 309, 267, 211, 91 (base); MS calcd for $C_{27}H_{31}O_7Si$ (M – *t*-Bu), 495.1839; found, 495.1838; $[\alpha]_D^{25} = -44.9°$ (c = 0.63, $CHCl_3$).

1β,3α-Specionin (33β) and 1β,3β-specionin (34β).

A solution of the silylated benzyl ethyl catalposide **30β** (8 mg, 0.014 mmol) in ethanol (0.25 mL) was added to mercury (II) acetate (5 mg, 0.016 mmol) and the mixture was stirred for 1 h at 25°C under argon atmosphere. The solvent was removed under reduced pressure, and the residue was dissolved in benzene (0.5 mL). Tri-*n*-butyltin hydride (5 μL, 0.02 mmol) was added to this solution at 0°C, and the mixture was allowed to stand for 30 min, during which time mercury could be seen to precipitate. The mixture was filtered through Celite with chloroform, and concentrated. After purification by MPLC (12% ethyl acetate/hexane), a 1:1 mixture of products **31β** and **32β** (5 mg, 60%), which was not chromatographically separable, was obtained. A solution of this mixture of epimers (5.5 mg, 0.009 mmol) in THF (0.5 mL) was stirred with tetra-*n*-butylammonium fluoride trihydrate (6 mg, 0.019 mmol) under argon atmosphere for 30 min at 25°C. The reaction mixture was diluted with ethyl acetate, filtered through Florisil, and concentrated. After purification by MPLC (45% ethyl acetate/hexane), the pure 1β,3α-epimer (2.0 mg, 45%) and 1β,3β-epimer (2.2 mg, 49%) were obtained: 1β,3α epimer; ^1H NMR δ 1.23 (t, 3H), 1.30 (t, 3H), 2.41-2.53 (m, 2H), 3.48-3.75 (m, 5H), 3.77 (s, 1H), 4.02-4.12 (m, 2H), 4.73 (d, 1H, J = 8.6 Hz), 5.01 (d, 1H, J = 2.7 Hz), 5.13 (s, 2H), 5.57 (d, 1H, J = 8.0 Hz), 6.99 (d, 2H, J = 9.0 Hz), 7.34-7.44 (m, 5H), 8.02 (d, 2H, J = 9.0 Hz); 1β,3β epimer; δ 1.23 (t, 3H), 1,30 (t, 3H), 1.67-1.86 (m, 2H), 2.43-2.57 (m, 2H), 3.48-3.69 (m, 4H), 3.71 (s, 1H), 3.94 (dq, 1H), 4.00-4.12 (m, 2H), 4.51 (d, 1H, J = 8.3 Hz), 4.66 (dd, 1H, J = 2.7, 9.2 Hz), 5.13 (s, 2H), 5.25 (d, 1H, J = 8.0 Hz), 6.99 (d, 2H), 7.31-7.45 (m, 5H), 8.01 (d, 2H).

A mixture of the 1β,3α epimer (2.0 mg, 0.004 mmol) and palladium on carbon (10% Pd, spatula tip) in ethanol (0.5 mL) was stirred under a hydrogen atmosphere for 45 min. The reaction mixture was diluted with ethyl acetate, and filtered through Florisil eluting with ethyl acetate. Crude **33β** (1.4 mg) was recovered in a good state of purity in 86% yield; IR (neat): 3362 (broad), 3030, 2995, 2928, 2865, 1700, 1653, 1608, 1559, 1516, 1447, 1381, 1354, 1277, 1165, 1099, 1022, 978, 914, 851, 804, 771, 700 cm^{-1}; ^1H NMR δ 1.27 (t, 3H), 1.35 (t, 3H), 1.78-1.88 (m, 2H), 2.39-2.59 (m, 3H), 3.44-3.68 (m, 3H), 3.74 (dq, 1H), 3.79 (s, 1H), 4.00-4.14 (m, 2H), 4.78 (d, 1H, J = 8.6), 5.06 (d, 1H, J = 2.5 Hz), 5.62 (d, 1H, J = 8.0 Hz), 6.90 (d, 2H), 8.02 (d, 2H); MS *m/e* (no M^+), 349, 303, 267, 251, 236, 230, 211, 199, 193, 164, 121 (base), 111, 93.; MS calcd for $C_{18}H_{21}O_7$ (M – OEt), 349.1287; found, 349.1286; $[\alpha]_D^{25} = -140.7°$ (c = 0.14, crude, $CHCl_3$).

Using the same procedure, crude **34β** (1.6 mg) was recovered in a good state of purity in 89% yield: IR (neat) 3370 (broad), 2926, 2865, 1717, 1700, 1684, 1653, 1636, 1609, 1593, 1559, 1539, 1516, 1456, 1379, 1277, 1165, 1115, 1030, 941, 905, 851, 804, 788, 689 cm^{-1}; ^1H NMR δ 1.23 (t, 3H), 1.30 (t, 3H), 1.66-1.88 (m, 2H), 2.51 (m, 2H), 3.48-3.69 (m, 3H), 3.72 (s, 1H), 3.95 (dq, 1H), 4.01-4.10 (m, 2H), 4.51 (d, 1H, J = 8.3 Hz), 4.66 (dd, 1H, J = 2.7 Hz, J = 9.0 Hz), 5.26 (d, 1H, J = 8.0 Hz), 6.87 (d, 2H), 7.97 (d, 2H); MS *m/e* (no M^+), 349, 317, 267, 251, 236, 230, 211, 199, 193, 182, 164, 121 (base); MS calcd for $C_{18}H_{21}O_7$ (M – OEt), 349.1287; found, 349.1286; $[\alpha]_D^{25} = -112.5°$ (c = 0.16, crude, $CHCl_3$)

6-*O*-Benzyl-10-*O*-*t*-butyldimethylsilyl specionin (32α).

To a solution of the olefin **30α** (6.2 mg, 0.011 mmol) in EtOH (4 mL) at room temperature was added $Hg(OAc)_2$ (4.6 mg, 0.014 mmol). The mixture was stirred for 30 min, then cooled to –78 °C. Next, 3 M NaOH (10 μL) and 0.5 M $NaBH_4$ (in 3 M NaOH, 28 μL) were added. After stirring for 1 h at –78 °C, the reaction mixture was treated with CH_2Cl_2 (6 mL) and saturated NH_4Cl (30 μL), and filtered through a Celite/Florisil pad. Flash chromatography (8% EtOAc/hexane) afforded 5.9 mg (70%) of pure product; IR (neat) 2930, 1713, 1605, 1252, 1102, 1026 cm^{-1}; ^1H NMR δ 8.03 (d, 2H, J = 8.8 Hz), 7.46-7.35 (m, 5H), 7.00 (d, 2H, J = 8.8 Hz), 5.37 (d, 1H, J = 8.5 Hz), 5.13 (s, 2H), 5.12 (d, 1H), 4.88 (dd, 1H, J = 7.0, 2.3 Hz), 4.18 (d, 1H, J = 11.9 Hz), 3.90-3.82 (m, 1H), 3.60 (s, 1H), 3.55 (d, 1H, J = 11.8 Hz), 3.51-3.47 (m, 1H), 2.83 (dd, 1H, J = 8.0, 4.0 Hz), 2.44-2.40 (m, 1H), 2.00-1.89 (m, 1H), 1.89-1.82 (m, 1H), 1.27-1.19 (2 overlapping t, 6H), 0.91 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); MS *m/e* 495, 294, 285, 211, 91 (base); MS calcd for $C_{27}H_{31}O_7Si$ [M – *t*-Bu)], 495.1839; found, 495.1838; MS (ammonia CI) *m/e* 599 (M+H), 581, 570, 553 (base), 535, 524, 507, 421, 325, 267, 246, 211, 91; $[\alpha]_D^{25} = -28.7°$ (c = 0.15, $CHCl_3$).

Specionin (4).

To a solution of **32α** (10 mg, 0.017 mmol) in THF (5 mL) was added $Bu_4NF{\cdot}3H_2O$ (6 mg, 0.019 mmol). The reaction mixture was stirred at ambient temperature. After 20 min, the reaction mixture was diluted with EtOAc, washed with water and brine, and dried over $MgSO_4$. The crude product was concentrated and dissolved in EtOH (5 mL). 10% Pd/C (14. 5 mg) was added and the reaction mixture was placed under a H_2 atmosphere. After 3 h under H_2, the reaction mixture was diluted with EtOAc and filtered through a Celite/Florisil pad with EtOAc. Flash chromatography (50% EtOAc/hexane) afforded 5.9 mg (90%) of pure specionin (**4**): IR (neat) 3353, 2926, 1711, 1609, 1593, 1277, 1235, 1165, 1121, 1071, 974 cm^{-1}; ^1H NMR δ 7.98 (d, 2H, J = 8.5 Hz), 6.87 (d, 2H, J = 8.6 Hz), 5.93 (br s, 1H), 5.38 (d, 1H, J = 8.3 Hz), 5.07 (d, 1H, J =

4.0 Hz), 4.90 (dd, 1H, J = 6.7, 2.6 Hz), 4.03 (dd, 1H, J = 12.5, 6.1 Hz), 3.90-3.72 (m, 3H), 3.79 (s, 1H), 3.57-3.44 (m, 2H), 2.82 (dd, 1H, J = 8.2, 4.0 Hz), 2.45 (m, 1H), 2.08-1.95 (m, 1H), 1.95-1.82 (m, 1H), 1.30-1.17 (2t, 6H); ^{13}C NMR δ 15.1, 15.3, 29.1, 33.1, 40.3, 60.6, 61.2, 63.1, 63.9, 66.6, 79.0, 93.8, 96.1, 115.3, 122.2, 132.2, 160.4, 166.6; ^{13}C NMR(CD_3OD) δ 15.5, 15.6, 30.3, 34.2, 41.2, 61.2, 61.4, 64.0, 64.8, 67.3, 80.7, 94.9, 97.8, 116.2, 122.0, 133.0, 163.8, 168.3; MS *m/e* 317, 236, 208, 105, 91 (base); MS calcd for $C_{17}H_{17}O_6$ [M – (EtOH + CH_2OH)], 317.1025; found, 317.1025; MS (ammonia CI) *m/e* 395 (M+H), 366, 349 (base), 320, 211, 193, 164, 121; TLC R_f = 1.0 (in MeOH), 0.68 (in ether), 0.63 (in EtOAc), 0.29 (in 50 % EtOAc/Hexane), identical R_f with natural specionin; $[\alpha]_D^{25}$ = –29.5° (c = 0.295, $CHCl_3$); $[\alpha]_D^{25}$ = –30.7° (c = 0.075, $CHCl_3$, natural specionin).

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References

1 a) Mellon Predoctoral Fellow, University of Pittsburgh. b) Council for Chemical Research Fellow, University of Pittsburgh. c) Recipient of a Sloan Foundation Fellowship, 1985-87; Dreyfus Teacher-Scholar, 1985-89; Eli Lilly Grantee, 1985-87. Merck Faculty Development Awardee, 1986-87. National Institutes of Health Research Career Development Awardee, 1987-92.

2 Reviews: Bobbitt, J. M.; Segebarth, K. P. "Cyclopentanoid Terpene Derivatives", Marcel Dekker: N.Y., 1969. El-Naggar, L. J.; Beil, J. L. *J. Nat. Products*, **1980**, *42*, 649.

3 There are several eight carbon iridoids and also some important fourteen carbon iridoids, see reference 2.

4 Sticher, O. "New Natural Products and Plant Drugs with Pharmacological, Biological, and Therapeutic Activity", Wagner, H. and Wolff, P., Eds.; Springer-Verlag: N.Y., 1977, p. 145.

5 a) Chang, C. C.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1983**, 605. b) Chang, C. C. Ph.D., Thesis, Columbia University, 1985. We thank Professor Nakanishi for a copy of this thesis. c)Although specionin is widely assumed to be an artifact of isolation, a recent deliberate attempt to convert catalposide to specionin by ethanolysis was not successful. Chan, T. H.; Zhang, Y. J.; Sauriol, F.; Thomas, A. W.; Strunz, G. M. *Can. J. Chem.* **1987**, *65*, 1853.

6 For reviews, see: Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41. Thomas, A. F.; Bessiere, Y. in "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley: N.Y., 1981; Vol. 4, pp 494-507.

7 Büchi, G.; Gulder, B.; Schneider, R. S.; Wilde, I. *J. Am. Chem. Soc.*, **1967**, *89*, 2776. The oxidative cleavage of diquinanes (as illustrated in Scheme 1) was first developed by Whitesell. Whitesell, J. A.; Helbing, A. M. *J. Chem. Soc., Chem. Commun.* **1977**, 554.

8 Büchi, G.; Carlson, J. A.; Powell, J. E., Jr.; Tietze, L.-F. *J. Am. Chem. Soc.* **1970**, *92*, 2165.

9 Callant, P.; Onega, R.; Vandewalle, M. *Tetrahedron* **1981**, *37*, 2085. Callant, P.; De Wilde, H.; Vandewalle, M. *Tetrahedron* **1981**, *37*, 2079. Callant, P.; Storme, P.; Van der Eycken, E.; Vandewalle, M. *Tetrahedron Lett.* **1983**, *24*, 5797.

10 For a recent preparation of the C-4 unsubstituted enol acetal by acetate pyrolysis, see: Trost, B. M.; Balkovec, J. M.; Mao, M. K.-T. *J. Am. Chem. Soc.* **1986**, *108*, 4974.

11 Tietze, L.-F. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 828. Schreiber, S. L.; Meyers, H. V.; Wiberg, K. B. *J. Am. Chem. Soc.* **1986**, *108*, 8275. Denmark, S. E.; Sternberg, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 8277.

12 Curran, D. P.; Jacobs, P. B. *Tetrahedron Lett.* **1985**, *26*, 2031. The *E* and *Z* stereochemical descriptor assignments of the ketene silyl acetals in this paper are reversed.

13 Weygand, F. *Methods Carbohydr. Chem.* **1967**, Vol. 1, 183.

14 Fraser-Reid, B.; McLean, A.; Usherwood, E. W.; Yunker, M. *Can. J. Chem.* **1970**, *48*, 2877.

15 a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. b) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48.

16 Wollenberg, R. H.; Goldstein, J. E. *Synthesis* **1980**, 757.

17 Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410.

18 Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

19 a) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024. b) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826.

20 Hine, J. "Structural Effects on Equilibria in Organic Chemistry" Wiley: N.Y., 1975. Hine, J.; Linden, S. M. *J. Org. Chem.* **1983**, *48*, 584, and previous papers in the series.

21 Similar observations have been made in related systems: Ireland, R. E.; Vevert, J.-P. *J. Org. Chem.* **1980**, *45*, 4260. Bartlett, P. A.; Pizzo, C. F. *J. Org. Chem.* **1981**, *46*, 3896.
22 The stereochemical outcome was confirmed by chemical correlation. Oxidation of **9a** to an enone (2LDA/2TMSCl; $Pd(OAc)_2$), followed by conjugate addition of lithium dimethylcuprate, gave **9b** as the sole product. The cuprate should attack the exo face of the bicyclic system.
23 Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.
24 a) Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, A. K.; Iyengar, R. *J. Org. Chem.* **1980**, *45*, 1185. b) Miyashita, M.; Yamaguchi, R.; Yoshikoshi, A. *J. Org. Chem.* **1984**, *49*, 2857.
25 Kovacs, G.; Galambos, G.; Juvancz, Z. *Synthesis* **1977**, 171. Trost, B. M.; Junghein, L. *J. Am. Chem. Soc.* **1980**, *102*, 7910. Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1717.
26 Brown, J. J.; Lenhard, R. H.; Bernstein, S. *J. Am. Chem. Soc.* **1964**, *86*, 2183.
27 Brown, L.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 3876.
28 Van der Eycken, E.; Callant, P.; Vandewalle, M. *Tetrahedron Lett.* **1985**, *26*, 367.
29 Boat-like conformers should also be considered. For a more complete analysis of the comformation of the pyran ring in these compounds, see reference 39.
30 Baker, R.; Brimble, M. A.; Robinson, J. A. *Tetrahedron Lett.* **1985**, *26*, 2115.
31 Rastetter, W. H.; Richard, T. J.; Lewis, M. D. *J. Org. Chem.* **1978**, *43*, 3163.
32 Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T.; Inoue, S.; Sugiura, S.; Kakoi, H. *J. Chem. Soc., Chem. Commun.* **1972**, 64.
33 Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
34 The temperature must be kept low to prevent reductive opening of the epoxide at the 2°-carbon. Such diols formed by higher temperature LAH reduction have the oxidation pattern of several important iridoids (see ref. 1).
35 Details are contained in the Thesis of P. B. Jacobs (University of Pittsbugh, 1986) and will be deposited with the Cambridge Crystallographic File.
36 Takahashi, M.; Suzuki, H.; Moro-Oka, Y.; Ikawa, T. *Chemistry Lett.* **1981**, 1435. Felföldi, K.; Bartók, M. *J. Organomet. Chem.* **1985**, *297*, C-37.
37 Smith, M.; Moffatt, J. G.; Khorana, H. G. *J. Am. Chem. Soc.* **1958**, *80*, 6204.
38 Larock, R. C. "Solvomercuration/Demercuration Reactions in Organic Synthesis" Springer-Verlag: Berlin, 1986.
39 a) Van der Eycken, E.; Van der Eycken, J.; Vandewalle, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1719. b) Van der Eycken, E.; De Bruyn, A.; Van der Eycken, J.; Callant, P.; Vandewalle, M. *Tetrahedron* **1986**, *42*, 5385.
40 Van der Eycken, E.; Janssens, A.; Vandewalle, M. *Tetrahedron Lett.* **1987**, *28*, 3519.
41 Curran, D. P.; Jacobs, P. B.; Elliott, R. L.; Kim, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 5280.
42 Brown, H. C.; Geoghegan, P. Jr. *J. Am. Chem. Soc.* **1967**, *89*, 1522.
43 For recent developments in formation of the glycoside linkage, see: Tietze, L.-F.; Fischer, R. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 888. Battersby, A. R.; Westcott, N. D.; Glüsenkamp, K. H.; Tietze, L.-F. *Chem. Ber.* **1981**, *114*, 3439.
44 Two new syntheses of specionin have recently been completed, see: Hussain, N.; Leonard, J. *Tetrahedron Lett.* **1987**, *28*, 4871. Whitesell, J. K.; Allen, D. E. *J. Am. Chem. Soc.* **1988**, *110*, 0000.
45 Experimental procedures are only provided for the intermediates on the direct path to specionin and its anomers. In general, procedures were similar for the α and β series. Differences are noted where applicable. Full details from all compounds can be found in the Theses of B. H. Kim (University of Pittsburgh, 1987) and P. B. Jacobs (University of Pittsburgh, 1986).