Asymmetric synthesis of lignans using oxazolidinones as chiral auxiliaries

James L. Charlton and Gaik-Lean Chee

Abstract: A simple procedure for the asymmetric synthesis of lignans via chiral β-benzyl-γ-butyrolactones has been developed. The key benzylbutyrolactone intermediates were efficiently synthesized using a six-step procedure, starting from 3,4-(methylenedioxy)cinnamic acid. The key step in this sequence was a highly diastereoselective alkylation of an *N*-acyloxazolidinone enolate. The resulting β-benzyl-γ-butyrolactones were subsequently transformed into the benzylidene lignans gossypifan and savinin (hibalactone) via aldol condensation–dehydration reactions, and into the dibenzylbutyrolactone lignan 4′-demethylyatein, through alkylation. Oxidation of 4′-demethylyatein with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded *cis*- and *trans*-benzylidenebenzylbutyrolactones, whereas oxidation with DDQ/TFA gave 4′-demethyldeoxyisopodophyllotoxin.

Key words: lignans, synthesis, asymmetric, biosynthesis, oxidation, benzylbutyrolactones.

Résumé : On a mis au point une méthode de synthèse simple des lignanes impliquant des β-benzyl-γ-butyrolactones chirales. On a synthétisé les intermédiaires benzylbutyrolactones clés d'une façon efficace en faisant appel à une procédure en six étapes, à partir de l'acide 3,4-(méthylènedioxy)cinnamique. L'étape clé de cette séquence est une alkylation hautement diastéréosélective d'un énolate *N*-acyloxazolidinone. Les β-benzyl-γ-butyrolactones qui en découlent sont ultérieurement transformées en benzylidènes des lignanes gossypifane et savinine (hibalactone) par le biais de réactions de condensation aldolique et de déshydratation et en lignane dibenzylbutyrolactone 4′-déméthylyatéine par alkylation. L'oxydation de la 4′-déméthylyatéine par la 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) conduit aux benzylidènebenzylbutyrolactones *cis* et *trans* alors que l'oxydation à l'aide de DDQ/TFA fournit de la 4′-démethyldéoxyisopodophyllotoxyine.

Mots clés : synthèse de lignanes, asymétrique, biosynthèse, oxydation, benzylbutyrolactones.

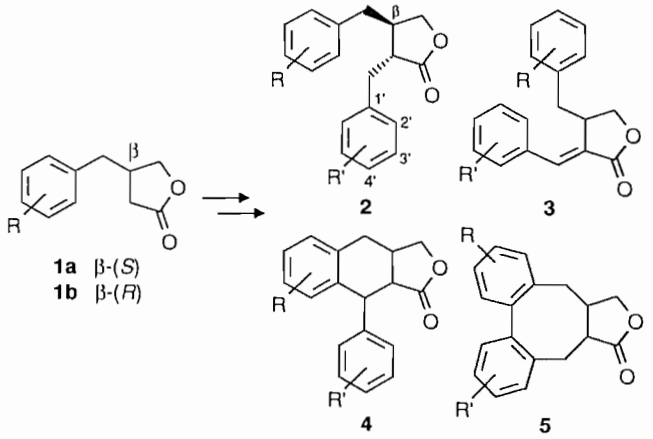
[Traduit par la rédaction]

Introduction

Many lignan natural products have interesting biological properties (1) and developing synthetic methods for this large class of compounds has been a challenge to synthetic chemists.[2] Many of the methods for the asymmetric synthesis of chiral lignans have involved the intermediacy of enantiomerically pure β-benzyl-γ-butyrolactones **1**. These have been used in the synthesis of dibenzylbutyrolactones **2**, benzylidenebenzylbutyrolactones **3**, aryltetralins **4**, and dibenzocyclooctadienes **5** (Scheme 1). In comparison to other general methods for lignan synthesis, using butyrolactones **1** as intermediates offers more structural variability than can be achieved otherwise.

Several synthetic approaches for the preparation of optically active butyrolactones having general structure **1** have been published. The first asymmetric synthesis of a butyrolactone of type **1b** (R = 3,4-methylenedioxy) was reported by Tomioka and Koga (3). In a lengthy procedure they diastereoselectively alkylated a chiral γ-substituted γ-butyrolactone followed by removal of the γ group. Posner et al. synthesized chiral benzylbutyrolactones by diastereoselective conjugate addition to an enantiomerically pure α-sulfinyl-γ-butenolide (4). Similar to the first example, the procedure is lengthy and the overall yield is relatively low. Yoda et al. carried out a conjugate addition on a chiral unsaturated lactam in the preparation of a butyrolactone of type **1b** (R = 3,4-methylenedioxy) (5). Once again, the yields for most steps were only moderate. An elegant catalytic asymmetric hydrogenation reaction was

Scheme 1.



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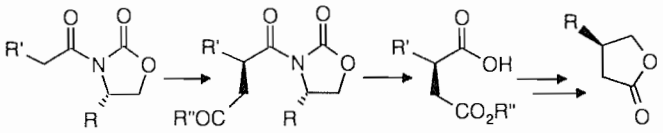
[2] Reviews on asymmetric synthesis of lignans: refs. 2*a*, 2*b*; Reviews on synthesis of lignans: refs. 2*c*–2*k*.

Scheme 2.



employed by Morimoto et al. to prepare **1a** and **1b** (R = 3,4-methylenedioxy and 3,4-dimethoxy) (6). Unfortunately, the chiral hydrogenation catalyst used by these authors is relatively unavailable. More recently, Honda et al. employed enantioselective deprotonation of a 3-benzylcyclobutanone in the synthesis of a lactone of type **1b** (R = 3,4-methylenedioxy) (7). Although only a few steps were involved in the synthesis, the enantioselectivity of the key reaction was moderate, affording **1b** in only 80% optical purity. Doyle et al. reported a novel and efficient synthesis of lactones **1a** and **1b** (R = H, 3-methoxy and 3,4-methylenedioxy) via an enantioselective intramolecular C-H insertion reaction of an alkyl diazoacetate (8). Chiral oxoimidazolidine carboxylate dirhodium catalysts were applied in the key reaction to afford a chiral benzylbutyrolactone in up to 94% ee, but neither the catalyst nor the chiral ligand that was used is commercially available. Two recent asymmetric syntheses of optically pure β-benzyl-γ-butyrolactones of structure **1a** (R = 3,4-dimethoxy and 4-methoxy) utilized an enzymatic transesterification of a prochiral diol (9). Although the process was highly enantioselective, relatively large amounts of the enzyme (lipase PS from *Pseudomonas fluorescens*) were needed.

Although the above reported methods have provided elegant routes to the preparation of lignan intermediates **1a** and **1b**, many problems still exist. These include laborious methods, poor overall yields, unsatisfactory enantiomeric purity, and (or) expensive reagents. A simple and efficient approach for the asymmetric synthesis of butyrolactones **1** is still required.

Substituted oxazolidinone heterocycles[3] are effective chiral auxiliaries giving excellent asymmetric induction in reactions such as alkylations, hydrogenations, and Diels–Alder reactions. Enolates derived from *N*-acyloxazolidinones can be alkylated with α-bromoacetate to afford diastereomerically pure substituted succinate derivatives (11). After the removal of the oxazolidinone chiral auxiliary, the chiral half acid can be reduced and lactonized to afford the β-substituted butyrolactone in high optical purity (Scheme 2) (11*a*).

We have adopted this simple and versatile method for the asymmetric synthesis of β-benzyl-γ-butyrolactones **11a** and **11b** (see Scheme 3). These were subsequently transformed into the lignans gossypifan (**14a**), savinin (hibalactone) (**14b**), and 4′-demethylyatein (**16**) (these are the first reported syntheses for gossypifan and 4′-demethylyatein) (Schemes 4 and 5).

4′-Demethylyatein (**16**) is considered to be a biosynthetic precursor to aryltetralin lignans having the podophyllotoxin pattern of substitution (see **23** in Scheme 7) (12). It has been proposed that oxidation to a quinone methide **20** is followed by cyclization to 4′-demethyldeoxypodophyllotoxin (the 1,2-*cis* isomer of **23**). Kende et al. were able to mimic the biosynthetic pathway and oxidatively cyclize a similar diarylbutane (13); however, attempts to cyclize 4′-demethylyatein itself have been unsuccessful (14*a*).[4] We have restudied the oxidation of this biologically important precursor using DDQ as oxidant. An aryltetralin lignan was successfully prepared and a better understanding of the biosynthesis of lignans was achieved.

Results and discussion

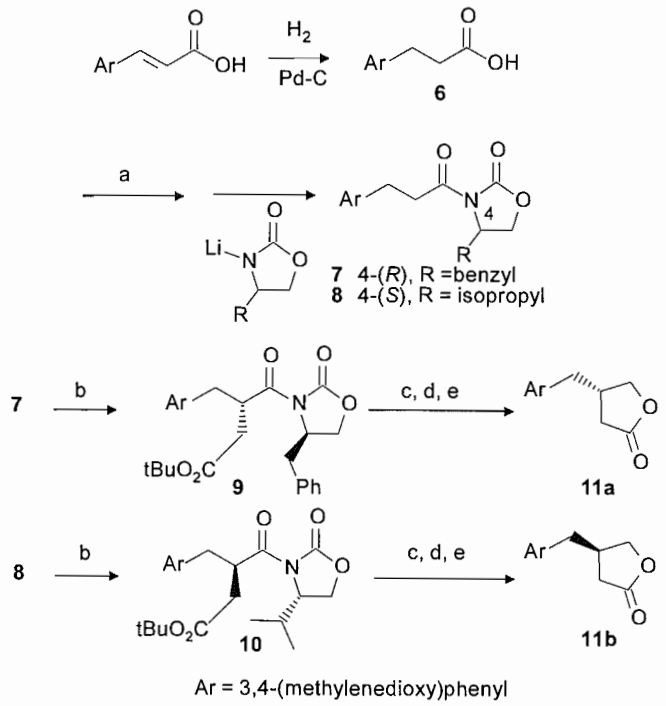
The enantiomerically pure (*S*)- and (*R*)-β-3,4-(methylenedioxy)benzyl-γ-butyrolactones (**11a** and **11b**) were efficiently synthesized in six steps from 3,4-(methylenedioxy)cinnamic acid, as shown in Scheme 3, in an overall yield of >45%. Dihydrocinnamic acid **6** was obtained in excellent yield from hydrogenation of commercially available 3,4-(methylenedioxy)cinnamic acid. Using a modified literature procedure (11), commercially available (4*R*)-benzyl and (4*S*)-isopropyl-2-oxazolidinone were *N*-acylated with dihydrocinnamic acid **6** to give N-acyloxazolidinones **7** and **8** in 88% and 84% yield, respectively. The *N*-acyloxazolidinones **7** and **8** were diastereoselectively alkylated with *tert*-butyl bromoacetate to afford one major diastereomer in each case (**9** and **10**, ca. 80% yield), having >95% diastereomeric excess as shown by the ^{1}H NMR spectrum. Although the absolute configuration could not be determined at this stage it was expected to be that shown in Scheme 3. The oxazolidinone chiral auxiliary was removed with LiOH–H_2O_2 without affecting the *tert*-butyl ester. The crude acid was reduced to an alcohol using BH_3·THF, then lactonized with TFA to afford the benzylbutyrolactone **11** in about 70% yield from the *N*-acyloxazolidinone. The benzylbutyrolactones **11a** and **11b** have optical activities and other spectroscopic characteristics consistent with the previously reported values (15). Based on their optical activity, the enantiomeric excesses of these lactones were >95%. The chiral auxiliaries, (4*S*)-isopropyl- and (4*R*)-benzyl-2-oxazolidinone, were readily recovered from the lactonized product by chromatography. Compared to previously reported methods, the present approach to the synthesis of β-benzyl-γ-butyrolactones is more efficient. It is simple, gives high asymmetric induction, and uses commercially available reagents.

Having obtained the enantiomerically pure butyrolactones **11a** and **11b**, their conversion to optically pure lignans was undertaken. The benzylidene lignans gossypifan (**14a**) and savinin (hibalactone) (**14b**) were synthesized from **11a** and **11b** following a modified literature procedure (16) as illustrated in Scheme 4. The β-benzyl-γ-butyrolactones **11a** and **11b** were each deprotonated with *N*-sodiohexamethyldisilazane (NaHMDS), and then treated with 3,4-dimethoxybenzaldehyde (for **11a**) and 3,4-(methylenedioxy)benzaldehyde (for **11b**) to afford aldol products **12a** and **12b**, which were acetylated in situ by adding a mixture of Ac_2O–DMAP–Et_3N to the reaction mixtures. The crude acetylated products **13a** and **13b** were then treated with DBU in refluxing toluene to produce the *trans*-benzylidene lignans gossypifan (**14a**) and savinin (**14b**) respectively, in >90% overall yield (from **11**). Gossypifan (**14a**) is a naturally occurring lignan recently isolated from a plant (*Jatropha gossypifolia*) and possesses medicinal and

[3] The use of oxazolidinones as chiral auxiliaries was recently reviewed in textbooks (refs. 10*a*–10*c*) and by Evans et al. (10*d*).

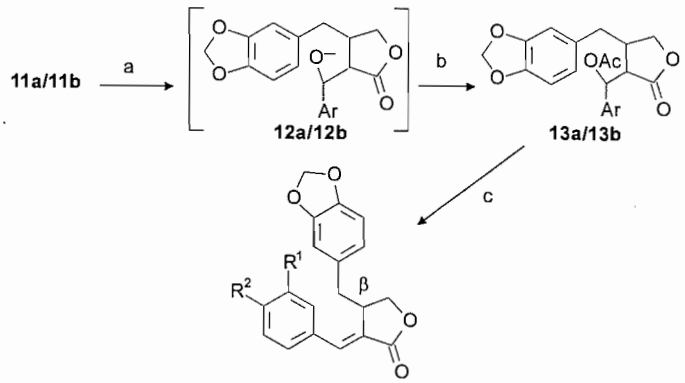
[4] The cyclization of yatein itself to aryltetralin and arylnaphthalene lignans has been more successful: see refs. 14*b*–14*d*.

Scheme 3.



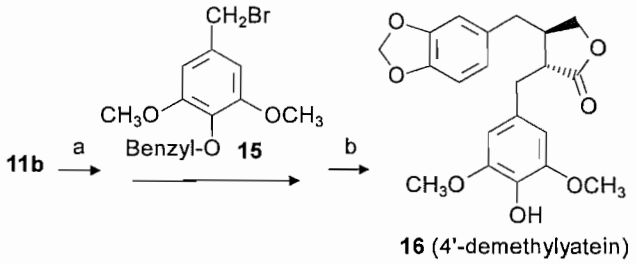
Key: (a) NEt_3, pivaloyl chloride; (b) NaHMDS, *tert*-butyl bromoacetate; (c) LiOH, H_2O_2, THF, H_2O; (d) BH3·THF; (e) TFA, CH_2CL_2.

Scheme 4.



Key: (a) NaHMDS, ArCHO; (b) Ac_2O, NEt_3, DMAP; (c) DBU

Scheme 5.



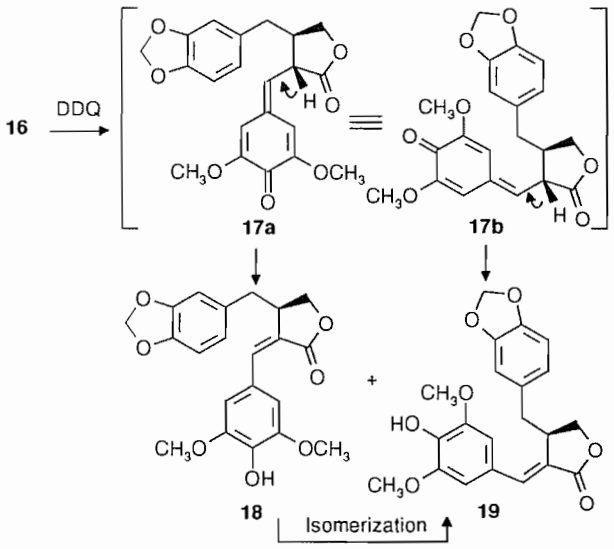
Key: (a) NaHMDS; (b) H_2, Pd-C.

pesticidal properties (17). The synthetic material, **14a**, had both rotation and other spectroscopic properties consistent with those reported for the natural product (17). This is the first reported synthesis of this compound. Savinin (also known as hibalactone (18*a*)) (**14b**), which is an insecticide synergist, also had properties consistent with those previously reported (18*b*, 18*c*). It should be noted that savinin has been previously prepared from **11b** by Honda et al. in four steps and 37% yield (7). The method of Tanaka et al. (16) that was used in the current work has the advantage that it is a one-pot procedure that gives savinin in 90% yield.

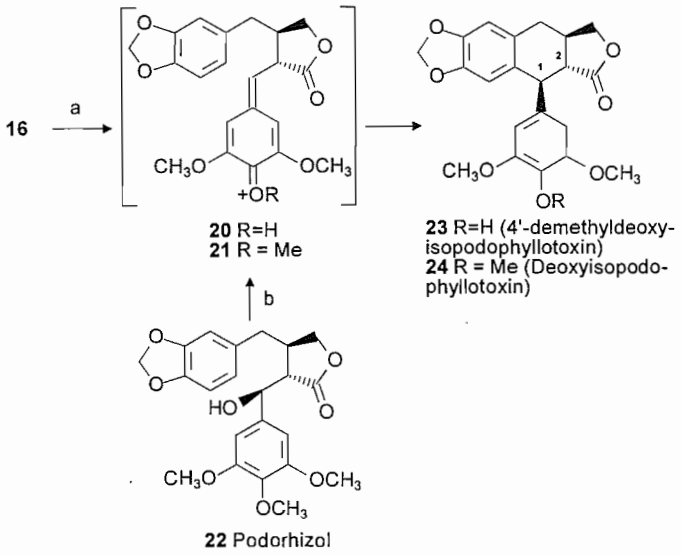
In addition to savinin, butyrolactone **11b** was also converted to 4′-demethylyatein (**16**), a naturally occurring dibenzylbutyrolactone lignan that has been regarded as a biosynthetic precursor to 4′-demethylpodophyllotoxin derivatives (12). The anion of butyrolactone **11b** was reacted with benzyl bromide **15**, which was, in turn, prepared from syringic acid by benzylation, reduction, and bromination (19). Careful control of the reaction temperature during benzylation of **11b** was necessary to prevent formation of the dibenzylated product. HMPA, often used for this type of benzylation, was not required for this reaction. The resulting crude 4′-benzylated yatein was hydrogenated to afford 4′-demethylyatein in an overall yield of 62% from **11b** (see Scheme 5). The synthetic 4′-demethylyatein had spectroscopic properties identical to those reported previously (20).

Previous attempts to oxidize racemic 4′-demethylyatein using metallic oxidants such as vanadium oxytrifluoride and thallium trifluoroacetate in order to induce cyclization to an aryltetralin lignan were totally unsuccessful (14*a*). On the other hand, Pelter et al. have reported a successful oxidative cyclization of a monophenolic lignan, which is structurally related to 4′-demethylyatein, using phenyliodonium bis(trifluoroacetate) (PIFA) as oxidant (21). The reaction afforded a mixture of dibenzocyclooctadiene diastereomers in good yield. In view of their success with the nonmetallic oxidant PIFA we decided to study the oxidation reaction of 4′-demethylyatein using DDQ. Oxidation of 4′-demethylyatein with DDQ in THF at room temperature resulted in the formation of a mixture of two compounds, *cis*- and *trans*-benzylidenelactones, **18** and **19**, in 95% total yield. The ratio of the *cis* to the *trans* isomer was about 1.3:1, as determined by ^{1}H NMR spectroscopy. The proposed elimination mechanism is shown in Scheme 6. Quinone methide **17** is considered to be the reactive intermediate. Elimination of a proton from **17** (from conformations **17a** and **17b**) could lead to **18** and **19**. It has previously been proposed that benzylidene lignans such as **18** and **19** (general structure **3**) may be formed biosynthetically via oxidation of dibenzylbutyrolactones **2** (12*a*). The oxidation result obtained for 4′-demethylyatein appears to confirm this possibility. After standing exposed to the air at room temperature for 2 weeks, *cis*-benzylidenelactone **18** isomerized completely to the *trans* isomer **19**. The isomerization process could also be achieved in 2 h by refluxing the *cis* and *trans* isomeric mixture with iodine in benzene, with UV irradiation. The isomerization process indicates the instability

Scheme 6.



Scheme 7.



Key: (a) DDQ, TFA.; (b) TFA.

of the *cis* isomer and may explain the lack of reports of isolation of *cis*-benzylidenelactone lignans from plants.

If quinone methide **17** were formed during oxidation of **16**, addition of acid might alter the course of the subsequent reactions of the quinone methide. Treating 4′-demethylyatein (**16**) with DDQ in the presence of TFA (see Scheme 7) resulted in the formation of 4′-demethyldeoxyisopodophyllotoxin (**23**), a naturally occurring all-*trans* aryltetralin lignan, in about 65% yield after preparative TLC and recrystallization. The concentration and the ratio of substrate to reagent were found to be very critical to the cyclization process. Protonated quinone methide **20** is proposed as the intermediate in the cyclization reaction. Friedel–Crafts substitution on the other aryl group leads to compound **23**. Notably, **23** has an all-*trans* geometry, in contrast to the podophyllotoxin type of stereochemistry (1,2-*cis*) often found in aryltetralin lignans formed biosynthetically.

An all-*trans* stereochemistry is also found in the product (see **24** in Scheme 7) obtained from the acid-catalysed cyclization of podorhizol (**22**) and structural analogues (12*a*). These reactions presumably involve the intermediate delocalized benzylic cation **21**, which is similar to **20** (Scheme 7).

To the best of our knowledge, the oxidative conversion of a monophenolic dibenzylbutyrolactone lignan to either an aryltetralin lignan or benzylidenebenzylbutyrolactone is unprecedented. Despite the fact that these reactions have been proposed biosynthetically they have not previously been demonstrated in the laboratory. Combining our current results with the earlier observations of Pelter et al. (21), it now seems reasonable to conclude that benzylidenebenzylbutyrolactone, aryltetralin, and dibenzocyclooctadiene lignans with 4′-hydroxyl groups (**3**, **4**, and **5** in Scheme 1) could all arise biosynthetically from a common 4′-hydroxydibenzylbutyrolactone precursor. The successful cyclization reaction of 4′-demethylyatein with DDQ–TFA has also provided a new method for the synthesis of aryltetralin lignans. Further investigations of structurally related compounds with other oxidants are in progress and will be reported in the near future.

Conclusion

A versatile asymmetric synthesis of β-benzyl-γ-butyrolactones, key intermediates in the synthesis of lignans, has been achieved using a six-step procedure, in an overall yield of >45% from 3,4-(methylenedioxy)cinnamic acid. The method afforded the β-benzyl-γ-butyrolactones in >95% optical purity. These intermediates were used in the synthesis of the benzylidene lignans gossypifan and savinin, and the dibenzylbutyrolactone lignan 4′-demethylyatein, in good to excellent yield. The DDQ oxidation of the latter product provides an alternative route for the preparation of aryltetralin lignans, and affords further substantiation of the proposed mechanism for the biosynthesis of lignans.

Experimental

General methods

The general experimental procedures and instrumentation have been described in a previous publication (22).

3,4-(Methylenedioxy)dihydrocinnamic acid (6)

3,4-(Methylenedioxy)cinnamic acid (1.86 g, 9.69 mmol) was dissolved in DMF (ca. 25 mL) and stirred with Pd–C (0.2 g) under H_2 (1 atm; 101.3 kPa) for 24 h. The suspension was filtered through Celite®, rinsing with water and EtOAc. The organic solution was separated, and the aqueous solution extracted with EtOAc (3 × 15 mL). The organic solutions were combined, washed with water (5 × 20 mL) to remove residual DMF, dried ($MgSO_4$), and concentrated under vacuum to afford a colorless crystalline solid (1.88 g, 100%): mp 82–84°C; IR (CH_2Cl_2): 3085 (COOH), 1711 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.64 (2H, t, J = 7.5), 2.88 (2H, t, J = 7.5), 5.92 (2H, s), 6.63–6.74 (3H, m); ^{13}C NMR ($CDCl_3$) δ: 30.3 (CH_2), 35.9 (CH_2), 100.8 (CH_2), 108.3 (CH), 108.7 (CH), 121.1 (CH), 133.9 (C), 146.0 (C), 147.6 (C), 179.1 (C); mass

spectrum *m/z* (relative intensity): 194 (M^+, 32), 176 (3), 149 (7), 135 (100); HRMS calcd. for $C_{10}H_{10}O_4$: 194.0579; found: 194.0570.

General procedure for the preparation of *N*-acyloxazolidinones 7 and 8

A modified literature procedure was used (11*b*). To a solution of 3,4-(methylenedioxy)dihydrocinnamic acid (**6**, 0.50 g, 2.53 mmol) in THF (6 mL) under N_2 at −70°C was successively added, dropwise, Et_3N (0.41 mL, 2.9 mmol) and pivaloyl chloride (0.32 mL, 2.6 mmol). The mixture was gradually warmed to 0°C, stirred for an hour, and then recooled to −70°C. *n*-BuLi (1.1 mL, 2.45 M in hexane, 2.6 mmol) was added dropwise to a solution of the (4*R*)-benzyl or (4*S*)-isopropyl-2-oxazolidinone (2.53 mmol) in THF (15 mL) under N_2 at −70°C. The resulting lithium salt was added dropwise to the above dihydrocinnamic acid mixture via a double-tipped needle at −70°C over a period of 15 min. The resulting mixture was stirred for an hour, and then warmed gradually to 0°C. After stirring at 0°C for 35 min, saturated aqueous NH_4Cl (2 mL) was added. The solution was concentrated under vacuum to remove most of the THF. Water (10 mL) was added and the solution was extracted with EtOAc (4 × 10 mL), dried ($MgSO_4$), and evaporated.

N-Acyloxazolidinone 7

Reacting dihydrocinnamic acid **6** and (4*R*)-benzyl-2-oxazolidinone as described above gave an oil (0.89 g) that slowly crystallized. Recrystallization from EtOAc–hexanes gave colorless crystals (0.78 g, 88%): mp 68–70°C; $[\alpha]_D^{20}$ −48 (*c* 0.30, $CHCl_3$): IR (CH_2Cl_2): 1783 and 1702 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.76 (1H, dd, *J* = 9.5, 13.4), 2.91–2.96 (2H, m), 3.13–3.32 (3H, m), 4.15–4.19 (2H, m), 4.66 (1H, m), 5.91 (2H, s), 6.71–6.76 (3H, m), 7.17 (2H, dd, *J* = 8.0, 1.67), 7.25–7.32 (3H, m); ^{13}C NMR ($CDCl_3$) δ: 30.0 (CH_2), 37.4 (CH_2), 37.8 (CH_2), 55.1 (CH), 66.2 (CH_2), 100.8 (CH_2), 108.2 (CH), 109.0 (CH), 121.3 (CH), 127.3 (CH), 128.9 (2 × CH), 129.4 (2 × CH), 134.2 (C), 135.2 (C), 145.9 (C), 147.6 (C), 153.4 (C), 172.3 (C); mass spectrum *m/z* (relative intensity): 353 (M^+, 40.5), 309 (4), 219 (5), 176 (34), 148 (82), 135 (100); HRMS calcd. for $C_{20}H_{19}O_5N$: 353.1263; found: 353.1263.

N-Acyloxazolidinone 8

Reacting dihydrocinnamic acid **6** and (4*S*)-isopropyl-2-oxazolidinone as described above gave an oil. This was chromatographed with 20% EtOAc–hexanes to afford a light yellow oil (0.65 g, 84%): $[\alpha]_D^{20}$ +61 (*c* 0.98, $CHCl_3$); IR (CH_2Cl_2): 1786 and 1708 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.84 (3H, d, *J* = 7.0), 0.90 (3H, d, *J* = 7.0), 2.35 (1H, dseptet, *J* = 3.9, 7.0), 2.90 (2H, m), 3.10–3.33 (2H, m), 4.22 (2H, m), 4.42 (1H, m), 5.91 (2H, s), 6.68–6.74 (3H, m); ^{13}C NMR ($CDCl_3$) δ: 14.6 (CH_3), 17.9 (CH_3), 28.4 (CH), 30.2 (CH_2), 37.4 (CH_2), 58.4 (CH), 63.4 (CH_2), 100.8 (CH_2), 108.2 (CH), 109.0 (CH), 121.3 (CH), 134.2 (C), 145.9 (C), 147.6 (C), 154.0 (C), 172.3 (C); mass spectrum *m/z* (relative intensity): 305 (M^+, 9), 180 (13), 179 (25), 178 (17), 176 (13), 149 (13), 148 (29), 135 (27); HRMS calcd. for $C_{16}H_{19}O_5N$: 305.1263; found: 305.1269.

General procedure for alkylation of *N*-acyloxazolidinones 7 and 8 with *tert*-butyl bromoacetate

This procedure is a modification of one found in the literature (11*b*). NaHMDS (2.10 mL, 1.0 M in THF, 2.10 mmol) was added dropwise to a solution of the *N*-acyloxazolidinone (2.0 mmol) in THF (15 mL) under N_2 at −73°C, over a period of 10 min. After stirring at −73°C for an hour, *tert*-butyl bromoacetate (0.92 mL, 6.30 mmol) was added dropwise. The mixture was stirred for 2 h before being quenched with saturated aqueous NH_4Cl (4 mL). It was concentrated under vacuum to remove most of the THF, and then diluted with EtOAc (15 mL) and water (10 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 10 mL). The organic solutions were combined, washed with saturated aqueous NH_4Cl (15 mL), 5% aqueous $NaHCO_3$ (15 mL), and brine (15 mL), dried ($MgSO_4$), and concentrated to afford a liquid that crystallized when triturated with hexane. The hexane washings were concentrated and chromatographed using hexanes–2-propanol (15:1) to give more product. The colorless solid was combined and recrystallized (see below).

Alkylated product 9

N-Acyloxazolidinone **7** (0.706 g, 2.0 mmol) was alkylated as above to give a colorless solid that was further recrystallized from MeOH (0.72 g, 77%): mp 138–139°C; $[\alpha]_D^{20}$ −98.5 (*c* 0.135, $CHCl_3$); IR (CH_2Cl_2): 1782, 1722, 1700 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.40 (9H, s), 2.36 (1H, dd, *J* = 4.1, 16.9), 2.51 (1H, dd, *J* = 9.3, 13.2), 2.75 (1H, dd, *J* = 9.9, 13.4), 2.80 (1H, dd, *J* = 10.9, 17.0), 2.97 (1H, dd, *J* = 5.7, 13.2), 3.32 (1H, dd, *J* = 3.2, 13.6), 4.03–4.15 (2H, m), 4.39 (1H, m), 4.60 (1H, m), 5.91 (2H, s), 6.67–6.79 (3H, m), 7.25–7.36 (5H, m); ^{13}C NMR ($CDCl_3$) δ: 28.1 (3 × CH_3), 36.5 (CH_2), 37.6 (CH_2), 37.8 (CH_2), 41.6 (CH), 55.5 (CH), 66.0 (CH_2), 80.8 (C), 100.9 (CH_2), 108.1 (CH), 109.6 (CH), 122.2 (CH), 127.2 (CH), 128.9 (2 × CH), 129.5 (2 × CH), 131.7 (C), 135.6 (C), 146.3 (C), 147.6 (C), 153.0 (C), 171.2 (C), 175.2 (C); mass spectrum *m/z* (relative intensity): 467 (M^+, 1), 411 (5), 234 (25), 192 (16), 135 (100), 92 (90); HRMS calcd. for $C_{26}H_{29}O_7N$: 467.1944; found: 467.1924.

Alkylated product 10

N-Acyloxazolidinone **8** (0.610 g, 2.0 mmol) was alkylated as above to give a colorless solid that was further recrystallized from EtOAc–hexanes (0.67 g, 80%): mp 123–124°C; $[\alpha]_D^{20}$ +92 (*c* 0.37, $CHCl_3$); IR (CH_2Cl_2): 1779 and 1723 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.90 (3H, d, *J* = 6.8), 0.93 (3H, d, *J* = 6.8), 1.39 (9H, s), 2.32 (1H, dd, *J* = 4.3, 16.8), 2.34 (1H, m), 2.47 (1H, dd, *J* = 9.3, 13.2), 2.74 (1H, dd, *J* = 10.5, 16.8), 2.94 (1H, dd, *J* = 5.8, 13.2), 4.15 (2H, m), 4.36 (2H, m), 5.96 (2H, s), 6.67 (1H, dd, *J* = 1.5, 7.9), 6.72 (1H, d, *J* = 7.9), 6.78 (1H, d, *J* = 1.5); ^{13}C NMR ($CDCl_3$) δ: 14.7 (CH_3), 18.0 (CH_3), 28.0 (3 × CH_3), 28.3 (CH), 36.6 (CH_2), 37.6 (CH_2), 41.5 (CH), 58.8 (CH), 63.2 (CH_2), 80.6 (C), 100.8 (CH_2), 108.1 (CH), 109.6 (CH), 122.2 (CH), 131.9 (C), 146.2 (C), 147.6 (C), 153.5 (C), 171.1 (C), 175.1 (C); mass spectrum *m/z* (relative intensity): 419 (M^+, 3), 363 (36), 346 (9), 304 (8), 303 (6), 234 (17), 206 (19), 175 (20), 149 (14), 135 (100); HRMS calcd. for $C_{22}H_{29}O_7N$: 419.1944; found: 419.1951.

General procedure for the preparation of benzylbutyrolactones 11a and 11b

A modification of a literature procedure was used (11*a*). The alkylated product (**9** or **10**, 1.40 mmol) was dissolved in THF (20 mL), and water was added (7.0 mL). The solution was

cooled to ice temperature, followed by addition of H_2O_2 (0.66 mL, 30% in H_2O, 5.8 mmol) and $LiOH \cdot H_2O$ powder (0.12 g, 2.8 mmol). The resulting mixture was stirred at 0–5°C for 1.5 h, then at room temperature (rt) for 3 h. After recooling to 0°C, saturated aqueous $NaHSO_3$ (2 mL), cold water (50 mL), and 2% HCl (2 mL) were added. The solution was carefully kept at 0°C during the additions to prevent hydrolysis of the *tert*-butyl ester. The resulting mixture was extracted with EtOAc (4 × 25 mL). The organic solutions were combined, washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and evaporated to give a liquid that was used in the following reaction without further purification. The crude liquid was redissolved in THF (25 mL) and cooled to 0°C. $BH_3 \cdot THF$ (1.68 mL, 1.0 M in THF, 1.68 mmol) was added dropwise to the acid solution over a period of 10 min. The resulting mixture was stirred at 0°C for 1 h, then at rt for 4 h. It was recooled to 0°C, MeOH (0.5 mL) added dropwise to destroy excess $BH_3 \cdot THF$, followed by cold water (10 mL) and 2% HCl (5 mL). The mixture was concentrated under vacuum to remove most of the THF. The remaining solution was extracted with EtOAc (3 × 15 mL). The combined EtOAc solution was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to afford a light brown liquid. The crude product was redissolved in CH_2Cl_2 (4 mL), cooled to 0°C, and TFA (4 mL) was added dropwise. The mixture was stirred for 1 h at ice temperature and for 3 h at rt, followed by concentration under vacuum with several coevaporations with benzene to remove all of the TFA. The resulting brown liquid was chromatographed with 20–33% EtOAc–hexanes.

(*S*)-(−)-Benzylbutyrolactone 11a

Alkylated product **9** (0.65 g, 1.4 mmol) was hydrolysed, reduced, and lactonized as described in the above general procedure to give, after chromatography, a light yellow liquid (0.215 g, 70% from **9**): $[\alpha]_D^{20}$ −4.8 (*c* 0.50, $CHCl_3$) (lit. (15) $[\alpha]_D^{20}$ −4.78 (*c* 1.14, $CHCl_3$)); NMR spectral data were consistent with those published previously (15).

(*R*)-(+)-Benzylbutyrolactone 11b

Alkylated product **10** (0.586 g, 1.4 mmol) was treated as above to afford a light yellow liquid (0.202 g, 66% from **10**): $[\alpha]_D^{20}$ +4.8 (*c* 0.665, $CHCl_3$) (lit. (15) $[\alpha]_D^{20}$ +4.87 (*c* 0.87, $CHCl_3$)); spectroscopic data were identical to those obtained from **11a**.

General procedure for preparation of benzylidenebenzylbutyrolactones 14a and 14b

A modified literature procedure was employed (16). To a solution of benzylbutyrolactone **11a** or **11b** (61 mg, 0.28 mmol) in THF (1 mL) under N_2 at −70°C was added NaHMDS (0.33 mL, 1.0 M in THF, 0.33 mmol) over a period of 5 min. The solution was stirred at −70°C for 15 min, then at −20°C (CCl_4 – Dry Ice) for 15 min to ensure complete deprotonation. The color of the solution changed from light yellow to intense bright yellow. The mixture was recooled to −70°C and a solution of a benzaldehyde (3,4-dimethoxybenzaldehyde for **11a**; 3,4-(methylenedioxy)benzaldehyde for **11b**) (0.28 mmol) in THF (1 mL) was added dropwise. After stirring at −70°C for 1.3 h, a mixture of Ac_2O (78 μL, 0.83 mmol), Et_3N (0.16 mL, 1.14 mmol), and DMAP (6 mg, 0.049 mmol) in THF (1 mL) was added dropwise to the reaction mixture. The resulting thick mixture was warmed to rt and stirred for 1.5 h before water (1 mL) was added. The solution was concentrated to remove most of the THF, diluted with water (5 mL) and 2% HCl (2 mL), and then extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 phases were washed with 2% HCl (3 × 5 mL), 5% aqueous $NaHCO_3$ (2 × 5 mL), and brine (10 mL), dried ($MgSO_4$), and concentrated under vacuum to give a foamy residue. The crude product was redissolved in toluene (3 mL), DBU (90 μL, 0.61 mmol) was added, and the solution was heated to 80°C. After 1.5 h the mixture was diluted with EtOAc (10 mL), washed successively with 2% HCl (2 × 5 mL), water (2 × 10 mL), and brine (15 mL), dried ($MgSO_4$), and evaporated to afford a yellow residue that crystallized on standing under vacuum.

Gossypifan (14a)

(*S*)-(−)-benzylbutyrolactone **11a** (0.61 g, 0.28 mmol) was hydroxyalkylated with 3,4-dimethoxybenzaldehyde (46 mg, 0.28 mmol), acetylated, and treated with DBU as described above. The crude product was chromatographed with EtOAc–hexanes (1:2) to afford a light yellow solid (95 mg, 92%): mp 143–146°C (lit. (17) mp 145–146°C); $[\alpha]_D^{20}$ 79.1 (*c* 0.110, $CHCl_3$) (lit. (17) $[\alpha]_D^{20}$ 82.4 (*c* 0.875, $CHCl_3$)). NMR spectral data were consistent with those published previously (17).

Savinin (14b)

(*R*)-(+)-Benzylbutyrolactone **11b** (0.61 g, 0.28 mmol) was hydroxyalkylated with 3,4-(methylenedioxy)benzaldehyde (42 mg, 0.28 mmol), acetylated, and treated with DBU as described above. The yellow residue crystallized upon standing under vacuum and was recrystallized from ethanol–chloroform to afford colorless crystals (89 mg, 90%): mp 139–142°C (lit. (18*b*), from benzene and ethanol, mp 146.4–148.4°C); $[\alpha]_D^{20}$ −82.9 (*c* 0.135, $CHCl_3$) (lit. (18*c*) $[\alpha]_D^{20}$ −82 (*c* 2.5, $CHCl_3$); lit. (18d) $[\alpha]_D^{20}$ −88 (*c* 1.0, $CHCl_3$)). NMR spectral data were consistent with those published previously (7).

Benzyl ester of *p*-*O*-benzyl syringic acid

A mixture of syringic acid (3.12 g, 15.7 mmol), benzyl bromide (5.6 mL, 47 mmol), and dry K_2CO_3 (11 g, 78 mmol) in acetone (80 mL) was refluxed under N_2 for 24 h. The resulting suspension was cooled to rt, concentrated under vacuum, diluted with water (100 mL), and extracted with CH_2Cl_2 (4 × 20 mL). The organic solution was dried ($MgSO_4$), concentrated, and chromatographed with hexanes and 6% EtOAc–hexanes to remove benzyl bromide. The product was eluted with EtOAc and concentrated to leave a colorless solid (5.70 g, 95%): mp 64–65°C; IR (CH_2Cl_2): 1714 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.85 (6H, s), 5.08 (2H, s), 5.35 (2H, s), 7.27–7.48 (12H, m); ^{13}C NMR ($CDCl_3$) δ: 56.2 (2 × CH_3), 66.8 (CH_2), 74.9 (CH_2), 107.0 (2 × CH), 125.2 (C), 127.9 (CH), 128.1$_3$ (2 × CH), 128.1$_6$ (2 × CH), 128.2 (CH), 128.4 (2 × CH), 128.6 (2 × CH) 136.1 (C), 137.3 (C), 141.1 (C), 153.2 (2 × C), 166.1 (C); mass spectrum *m/z* (relative intensity): 378 (M^+, 4), 287 (6), 181 (6), 149 (7), 105 (11), 91 (100); HRMS calcd. for $C_{23}H_{22}O_5$: 378.1467; found: 378.1463.

p-*O*-Benzyl syringyl bromide (15)

To a solution of the benzyl ester of *p*-*O*-benzyl syringic acid (0.919 g, 2.43 mmol) in THF (10 mL) under N_2 at ice temperature was carefully added $LiEt_3BH$ (7.0 mL, 0.8 M in THF,

5.6 mmol). The resulting mixture was stirred for 2 h and then 10% HCl (15 mL) was slowly added. The solution was concentrated under vacuum, diluted with water (10 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed successively with 5% HCl (3 × 20 mL), 5% aqueous $NaHCO_3$ (2 × 20 mL), and brine (20 mL). It was then dried ($MgSO_4$) and concentrated to afford an oil. The crude product (0.893 g) was redissolved in anhydrous ether (10 mL), followed by addition of pyridine (0.6 mL) and PBr_3 (0.55 mL, 5.79 mmol). The resulting colorless suspension was stirred for 2.5 h before filtering through Celite®. The filtrate was diluted with CH_2Cl_2 (10 mL), washed with 3% HCl (3 × 20 mL), water (2 × 20 mL), and brine (25 mL), then dried ($MgSO_4$), concentrated, and chromatographed (6–15% EtOAc–hexanes) to give a colorless liquid (0.53 g, 65%) that slowly solidified on standing: mp 53–55°C (lit. (19*b*) mp 40–42°C); IR (CH_2Cl_2): 1593, 1503, 1461, 1336, 1130 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.82 (6H, s), 4.45 (2H, s), 4.99 (2H, s), 6.60 (2H, s), 7.25–7.35 (3H, m), 7.48 (2H, dd, J = 8.1, 1.7); ^{13}C NMR ($CDCl_3$) δ: 34.3 (CH_2), 56.1 (2 × CH_3), 75.0 (CH_2), 106.2 (2 × CH), 127.8 (CH), 128.1 (2 × CH), 128.4 (2 × CH), 133.2 (C), 137.1 (C), 137.7 (C), 153.5 (2 × C); mass spectrum *m/z* (relative intensity): 338 ($M^+(^{81}Br)$, 0.1), 336 ($M^+(^{79}Br)$, 0.1), 148 (22), 136 (12), 91 (100); HRMS calcd. for $C_{16}H_{17}O_3{}^{79}Br$: 336.0361; found: 336.0333.

4′-Demethylyatein (16)

(*R*)-(+)-Benzylbutyrolactone **11b** (86 mg, 0.39 mmol) in THF (1.5 mL) under N_2 was cooled to −72°C. NaHMDS (0.45 mL, 1.0 M in THF, 0.45 mmol) was then added dropwise over a period of 10 min. The mixture was stirred at that temperature for 15 min, then at −20°C (CCl_4 – Dry Ice) for 25 min. It was recooled to −72°C and a solution of syringyl bromide **15** (0.135 g, 0.40 mmol) in THF (2 mL) was added. After stirring at −72°C for 5 h, the reaction mixture was quenched with 5% aqueous NH_4Cl (1 mL). The mixture was concentrated, diluted with 2% HCl (10 mL), and extracted with CH_2Cl_2 (3 × 7 mL). The organic fractions were combined, washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to afford an oil (0.20 g). The crude product was redissolved in EtOAc and stirred with Pd–C (40 mg) under H_2 overnight. The suspension was filtered through Celite® and the filtrate was concentrated and chromatographed (50% EtOAc–hexanes) to afford an oil (93 mg, 62%): $[\alpha]_D^{20}$ −25.8 (*c* 0.225, CH_2Cl_2): (lit. (20) $[\alpha]_D^{20}$ −25 (*c* 0.32, CH_2Cl_2)). NMR spectral data were consistent with those published previously (20).

***trans*-Benzylidene, 19**

To 4′-demethylyatein (**16**, 20 mg, 0.052 mmol) in THF (1 mL) was added dropwise a solution of DDQ (14 mg, 0.062 mmol) in THF under N_2. A temporary blue color appeared after each addition of the DDQ solution. The resulting mixture was stirred for 12 h and worked up by adding saturated aqueous $NaHSO_3$ (1 mL) and 2% HCl (2 mL), and extracting with EtOAc (3 × 5 mL). The organic solutions were combined, washed with 5% aqueous $NaHCO_3$ (5 × 5 mL), water (10 mL), and brine (10 mL), dried ($MgSO_4$), and concentrated to afford a light yellow oil (22 mg). The crude product contained two compounds, the *cis*- and *trans*-benzylidenes **18** and **19**, respectively, in a 1.3:1 ratio as determined by ^1H NMR spectroscopy. After standing exposed to the air at rt for about 2 weeks, the crude product was found to contain only the *trans* isomer **19**, as indicated by the ^1H NMR spectrum. This product resisted crystallization. It was purified by chromatography (EtOAc–hexanes 1:2 ratio) to afford an oil that slowly solidified (18 mg, total 95% from 4′-demethylyatein). The isomerization process observed above was also achieved by refluxing a crude product mixture of **18** and **19** (2 mg) in benzene (1.5 mL) in the presence of I_2 (1 mg), for 1.5 h, with UV irradiation for the first 10 min of reflux. The light pink solution was worked up by adding saturated aqueous $NaHSO_3$ (0.5 mL) and extracting with EtOAc (3 × 5 mL). The extract was dried ($MgSO_4$) and evaporated to give a light yellow residue (1.7 mg, 85%) that contained only *trans* isomer **19**, as shown by the ^1H NMR spectrum: mp 130–132°C; $[\alpha]_D^{20}$ −54 (*c* 0.31, $CHCl_3$); IR (CH_2Cl_2): 3529 (OH), 1748 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.65 (1H, dd, J = 10.0, 14.5), 3.04 (1H, dd, J = 4.6, 14.5), 3.84 (1H, m), 3.92 (6H, s), 4.23–4.32 (2H, m), 5.92 (2H, AB, Δδ = 2.4, J = 1.4), 6.61 (2H, m), 6.71 (1H, d, J = 7.9), 6.81 (2H, s), 7.50 (1H, d, J = 1.8); ^{13}C NMR ($CDCl_3$) δ: 37.6 (CH_2), 39.6 (CH), 56.4 (2 × CH_3), 69.6 (CH_2), 101.1 (CH_2), 107.2 (2 × CH), 108.4 (CH), 109.0 (CH), 121.8 (CH), 125.4 (C), 125.5 (C), 131.3 (C), 136.9 (C), 137.9 (CH), 146.6 (C), 147.2 (2 × C), 148.0 (C), 172.5 (C); mass spectrum *m/z* (relative intensity): 384 (M^+, 11), 249 (90), 189 (14), 135 (100); HRMS calcd. for $C_{21}H_{20}O_7$: 384.1209; found: 384.1222.

4′-Demethyldeoxyisopodophyllotoxin (23)

To 4′-demethylyatein (**16**, 35 mg, 0.091 mmol) in THF (3 mL) at 4°C was added TFA (24 μL, 0.31 mmol), followed by a solution of DDQ (42 mg, 0.185 mmol) in THF (1 mL). The solution became green for more than 1.5 h. It was stirred at ice temperature for 1.5 h, then at rt overnight. The color of the solution became deep red after stirring overnight. The reaction mixture was diluted with saturated aqueous $NaHSO_3$ (1 mL), concentrated to remove most of the THF, and diluted again with 5% aqueous $NaHCO_3$ (5 mL). The resulting bright yellow solution was extracted with CH_2Cl_2 (4 × 5 mL). The combined CH_2Cl_2 extracts were washed with 5% aqueous $NaHCO_3$ (5 × 5 mL) and water (10 mL), dried ($MgSO_4$), and concentrated to afford a light yellow solid (35 mg) that was sparingly soluble in EtOAc, Et_2O, and MeOH, but more soluble in CH_2Cl_2 and $CHCl_3$. Recrystallization of the crude solid from CH_2Cl_2 gave fine colorless needles (25 mg, 71%). The recrystallized product, analysed by ^1H NMR, was shown to be contaminated with an unknown component (ca. 5%) that could not be eliminated even after multiple recrystallizations from CH_2Cl_2. This by-product was removed by preparative TLC using a solvent mixture of $CHCl_3$–MeOH–AcOH (25:1:1) to yield a colorless solid (22 mg, 65% from 4′-demethylyatein); mp 282–285°C (lit. (15*a*) mp 285–287°C); $[\alpha]_D^{20}$ −77 (*c* 0.26, $CHCl_3$) (lit. (15*a*) $[\alpha]_D^{20}$ −81)). NMR spectral data were consistent with those published previously (15*a*).

Copies of ^1H and ^{13}C NMR spectra of all compounds have been deposited as supplementary material.[5]

[5] This material may be purchased from: The Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, Canada K1A 0S2.

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