Enantioselective synthesis of peperomins A, C, D, and analogs — Examination of diastereoselective cuprate conjugate additions to *N*-enoyl-4-diphenylmethyl-2-oxazolidinones

Mukund P. Sibi, Michael D. Johnson, and T. Punniyamurthy

Abstract: A concise and general route to secolignans has been developed. The first total synthesis of secolignans peperomin A (**1a**), peperomin C (**1b**), and peperomin D (**1c**) was accomplished in ~28% overall yield over five synthetic steps. Peperomin analogs (**1d**) and (**1e**), possessing two differentially substituted aryl groups, were synthesized by a highly selective conjugate addition. The overall yield for the analogs **1d** and **1e** were 27 and 26%, respectively.

Key words: peperomins, secoliganans, conjugate additions, 4-diphenylmethyl-oxazolidin-2-one.

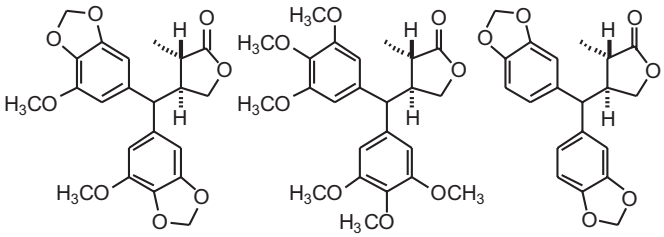
Résumé : On a mis au point une voie d'accès concise et générale conduisant aux sécolignanes. On a réalisé la première synthèse totale des sécolignanes pépéromine A (**1a**), pépéromine C (**1b**) et pépéromine D (**1c**), avec un rendement global d'environ 28% sur cinq étapes. Les analogues **1d** et **1e** de la pépéromine qui possèdent deux groupes aryles substitués de façon différente ont aussi été synthétisés par le biais d'une addition conjuguée hautement sélective. Les rendements globaux des synthèses des analogues **1d** et **1e** sont respectivement de 27 et 26%.

Mots clés : pépéromines, sécolignanes, additions conjuguées, 4-diphénylméthyloxazolidin-2-one.

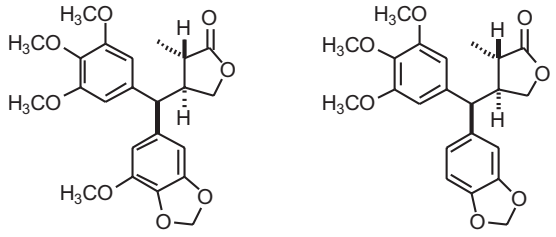
[Traduit par la Rédaction]

Introduction

Recently, a novel and unusual class of lignans were isolated from *Peperomia japonica* Makino by Chen et al. (1). Three lignans, peperomins A, B, and C, with a novel seco structure, were isolated from this perennial herb. Peperomin D was also recently isolated from *Peperomia glabella* (2). The use of aqueous and alcoholic decoctions of the herb as folk medicine for the treatment of malignant tumors has been noted (1). Two other secolignans with insect antifeedant activity have also been isolated from *Peperomia dindigulensis* (3). These secolignans have structural features that are present in the combretastatins (4) and podophyllotoxin (5). In view of the high tubulin inhibitory activity of the combretastatins and podophyllotoxin, the evaluation of the biological activity of peperomins and their analogs could be important. The structure-activity relationship in this novel secolignan series could shed more light on the conformational requirements for tubulin binding at the colchicine–podophyllotoxin site. Towards this end we have started a program on the preparation and biological evaluation of peperomins and analogs. Only a single racemic synthesis of peperomin C has been reported in the literature so far (6). This paper describes the first total synthesis of peperomins A, C, D, and two analogs.



1a Peperomin A **1b Peperomin C** **1c Peperomin D**



1d Peperomin analog **1e Peperomin analog**

We have been investigating methodologies for the preparation of succinates with various substituents on the carbon backbone and their application to the synthesis of butyrolactone

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[2]Taken in part from the M.S. thesis of M.D. Johnson, North Dakota State University, Fargo, North Dakota, October 1998.

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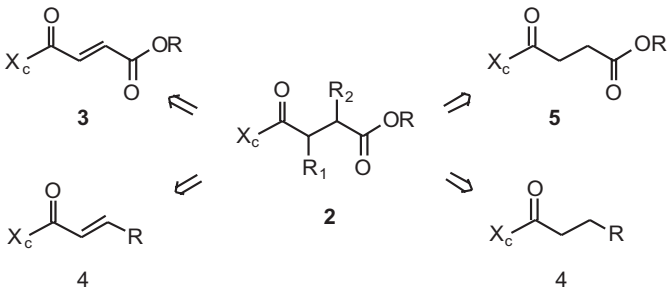
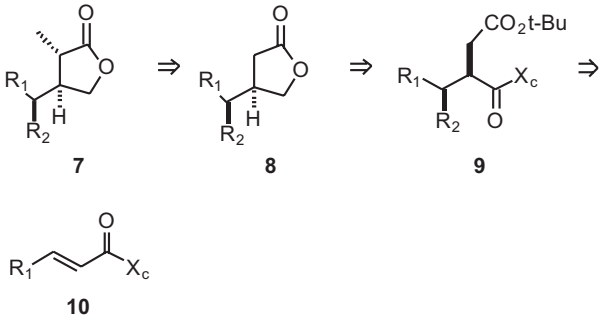
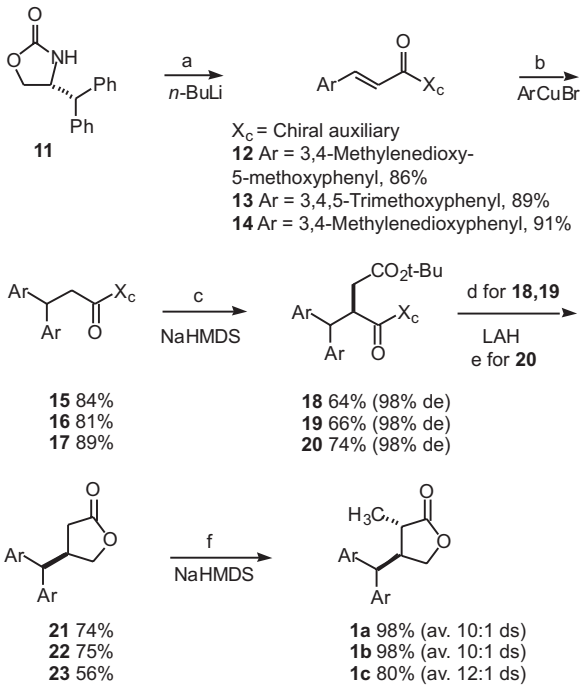
Scheme 1.



Scheme 2.



Scheme 3.



Key: (a) 1.0 equiv. n-BuLi, 1.1 equiv. ClCOAr, -78°C, 3h, THF; (b) (i) 3.1 equiv. Mg, (ii) 3.0 equiv. ArBr, (iii) 1.5 equiv. CuBr-$(CH_3)_2S$, -48 to 0°C, 3 h, 3:1 THF-$(CH_3)_2S$; (c) (i)1.1 equiv. NaHMDS, (ii)1.5 equiv. *t*-BuO_2CCH_2I,-78 to -48°C, 6 h, THF; (d) (i) 5.0 equiv. LAH (1 M), 20 h, THF, (ii) Silica gel; (e) (i) $LiOH/H_2O_2$; (ii) BH_3, (iii) PTSA; (f) (i)1.1 equiv. NaHMDS, (ii)1.5 equiv. CH_3I, 3 h, -78°C.

natural products (Scheme 1) (for other selected approaches to substituted succinates see refs. 7*a–c*; for an example of enolate alkylation leading to similar structures see ref. 7*d*). Recently, we described a novel route to paraconic and lignan natural products by the conjugate addition of radical intermediates starting from fumarates (**3** → **2**) (8). We have also reported on alternate routes to paraconic acids using succinates as starting materials (**5** → **2**) (9). The chiral auxiliary appended β-aryl propionates have also served as starting materials in the synthesis of lignan natural products (**6** → **2**) (10). These three disconnections, however, were not suited for the preparation of the secolignans and an alternate approach (**4** → **2**) was required.

The synthetic strategy for the preparation of peperomins is shown in Scheme 2. The design is based on the conjugate addition of an aryl group to the enoyloxazolidinone **10** (X_c = chiral auxiliary). The conjugate addition is followed by electrophile incorporation in a step-wise manner to furnish **9**. The strategy provides the flexibility for the introduction of different aryl groups by either varying the nucleophile or the enoyloxazolidinone leading to a variety of β,β-diaryl propionic acids (for procedures describing methodologies for the synthesis of enantiomerically enriched 3,3-diaryl propanoic acids and derivatives see refs. 11*a–f*; for a recent effort see ref. 11*g*). The next step in the sequence involves chemoselective reduction of the carbonyl bearing the chiral auxiliary and cyclization to provide **8**. Enolate alkylation of **8** from the less-hindered face establishes the required *trans* stereochemistry in the natural products. The key bond construction in our synthesis is a conjugate addition of an aryl copper reagent to a chiral enoate. Of the variety of chiral auxiliaries examined for conjugate additions, the oxazolidinones have generally been inferior in terms of selectivity. Recently, several groups have undertaken a study of various auxiliaries in the addition of copper reagents to enoates (for a comparative study of chiral auxiliaries see ref. 12). Hruby and co-workers (13; for NMR studies see ref. 13*b*) have shown that the oxazolidinone derived from phenylglycinol provides high selectivity in the addition of aryl coppers to cinnamates. We describe the use of an oxazolidinone derived from diphenylalanine in conjugate additions to acyclic systems using copper nucleophiles and determine its effectiveness in controlling stereochemistry at the β-carbon with the traditional oxazolidinones.

Results and discussion

Initial targets for examining the feasibility of our methodology were the simpler peperomins A, C, and D, since these compounds do not possess a chiral center at the benzylic carbon. This would allow us to establish reaction conditions for the conjugate additions (protocols for conjugate additions to enoyloxazolidinones has been established, see ref. 14*a*; for other contributions from the Hruby group see ref. 14*b*; 14*c–h*; for work on superquat oxazolidinone auxiliaries see ref. 14*i*). The synthesis of peperomin A, C, and D started with the acylation of the 4-diphenylmethyl-2-oxazolidinone auxiliary developed in our laboratory (Scheme 3) (15).[3] Treatment of **11** with *n*-BuLi provided the anion which was acylated with 3-[3′,4′-methylenedioxy-5′-methoxy-phenyl]-2-propenoyl

[3] For the synthesis of chiral auxiliary **11** see ref. 15*a*. This chiral auxiliary is available commercially from Aldrich Chemical Company; see ref. 15*b*. For the application of this auxiliary in synthesis see ref. 15*c*.

chloride (16).[4] 3,4-(Methylenedioxy)-5-methoxybenzaldehyde was transformed into the corresponding acid chloride: (*a*) $Ph_3P{=}CHCO_2Et$ (1.1 equiv), 70°C, 16 h, C_6H_6, 92% (96% *E*-isomer); (*b*) (*i*) 2.2 equiv NaOH, reflux, 20 min, 99%; (*ii*) 3.2 equiv oxalyl chloride, 25°C, 3 h, 93%. to furnish **12** in high yield. The required cinnamic acid (17) was prepared by HWE reaction between 3,4-methylenedioxy-5-methoxybenzaldehyde (18) and phosphanoacetic acid. Cinnamates **13** and **14** were prepared in high yields using 3-[3′,4′,5′-trimethoxyphenyl]-2-propenoyl chloride and 3-[3′,4′-methylenedioxyphenyl]-2-propenoyl chloride and lithiated **11**, respectively. The two-step protocol for the introduction of the substituents was then undertaken (19).[5] Reaction of **12** with the copper reagent prepared from 3,4-methylenedioxy-5-methoxy bromobenzene (20) gave **15** in 84% yield. Similarly, treatment of **13** and **14** with the copper reagent derived from 3,4,5-trimethoxy bromobenzene and 3,4-methylenedioxy bromobenzene (21) gave **16** and **17**, respectively. The next step involved the introduction of the acetic acid chain. This was accomplished in respectable chemical yield and excellent diastereoselectivity (>98%) by treatment of **15** and **16** with sodium hexamethyldisilazide followed by quenching of the sodium enolate with *tert*-butylbromoacetate. The diastereoselectivity in the alkylation step was established by ^1H NMR analysis (400 MHz) of the crude product. The alkylation of **17** using bromo-*tert*-butylacetate gave moderate yields (60%). A change of the leaving group to an iodo group gave **20** in higher yields (74%). Similar small increments in chemical efficiency were also noted for simple substrates as well as the alkylation precursor for peperomin analogs (vide infra). Thus, the iodoacetates were used in all the alkylation reactions (for a recent example of variation in chemical efficiency and selectivity in enolate alkylations with haloacetates see ref. 22).

With the desired succinates at hand, chemoselective reduction of the carbonyl attached to the chiral auxiliary was achieved by using LAH at low temperatures (23). Work-up of the reduction product followed by silica gel column chromatography furnished the butyrolactones **21** and **22** directly in good yields over two steps.[6] Reduction of **20** using LAH was not clean, providing the desired alcohol as well as an over-reduced diol (reduction of imide as well as the ester). Thus, an alternate sequence was devised. The chiral auxiliary in **20** was selectively hydrolyzed using $LiOH–H_2O_2$ (24). The resulting acid ester was reduced chemoselectively using borane (25). Lactonization using catalytic amounts of *p*-toluenesulfonic acid gave **23**. The three-step sequence could be carried out with good efficiency without isolation of the intermediates.

Introduction of the 3-substituent in butyrolactones by enolate alkylation has been well established in the literature (for some examples of diastereoselective alkylation at the 3-position see ref. 26). Generation of the sodium enolate of **21** and quenching with methyl iodide gave a 10:1 to 12:1 mixture of the methylated product. The use of LDA as the base in the alkylation gave a 8:1 mixture of the alkylated products (stereoselectivity of alkylations in substituted butyrolactones has been examined, see ref. 27). Attempts to improve diastereoselectivity by variation of reaction conditions were unrewarding. The two diastereomers were inseparable by chromatographic methods. However, the major diastereomer (**1a**) could be separated and purified by careful recrystallization. The major diastereomer was established to posses the 3,4-*trans* stereochemistry by comparison of its spectral data with those reported for peperomin A (1). The synthesis of **1b** followed a similar reaction sequence but starting with **22** and spectral data of the major diastereomer (~10:1 ds) was consistent with those reported for peperomin C (1). The overall yields for peperomin A (**1a**) and peperomin C (**1b**) were 28% (five steps) and 28% (five steps), respectively. The alkylation of **23** using NaHMDS as the base gave peperomin D (**1c**) with moderate to good diastereoselectivity and chemical yield. The spectral characteristics of the synthetic material were consistent with those reported in the literature for the natural product (2). The overall yield for peperomin D (**1c**) is ~27% over seven steps.

The synthesis of peperomin analogs (**1d** and **1e**) required the development of a diastereoselective conjugate addition protocol using copper reagents. Several groups have recently compared the effectiveness of different auxiliaries in conjugate additions and noted that the camphor sultams are quite good (28).[7] Hruby and co-workers (see ref. 13. For selected examples from a large body of work see ref. 29)[8] have also demonstrated that an oxazolidinone derived from phenylglycinol is an excellent chiral auxiliary in conjugate addition to enoates using organocuprates as nucleophiles. We have recently shown that a chiral auxiliary derived from diphenylalanine is superior to Evans-type oxazolidinones in conjugate radical additions (30). Thus, we wished to briefly evaluate the utility of this auxiliary in conjugate addition using cuprates as nucleophiles. The protocol developed by Hruby and co-workers was adapted as the standard reaction conditions (the addition of Grignard reagent with the use of copper bromide – dimethyl sulfide complex as the copper source). Reactions with a variety of substrates with simple as well as more functionalized aromatic nucleophiles were investigated. Results from these experiments are shown in Table 1. The diastereoselectivity in the conjugate additions was determined by NMR and HPLC analyses. The data in the table indicates that the diastereoselectivity was very high. The addition of Grignard reagent derived from 3,4-methylenedioxy-5-methoxy-

[4] 3,4-(Methylenedioxy)-5-methoxybenzaldehyde was transformed into the corresponding acid chloride: (*a*) $Ph_3P{=}CHCO_2Et$ (1.1 equiv), 70°C, 16 h, C_6H_6, 92% (96% *E*-isomer); (*b*) (*i*) 2.2 equiv NaOH, reflux, 20 min, 99%; (*ii*) 3.2 equiv oxalyl chloride, 25°C, 3 h, 93%.

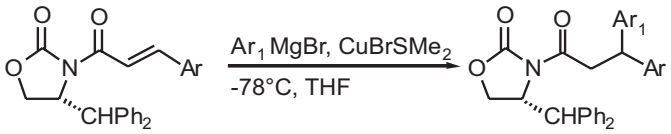
[5] For a review on enantioselective conjugate addition see ref. 19*b*. For other recent reviews see ref. 19*c*.

[6] The chiral auxiliary was recovered in >95% yield.

[7] (*S*)-4,4-Dimethylpyroglutamate as a chiral auxiliary, see ref. 28*a*. Addition of Yamamoto's reagent with high selectivity to *N*-enoyloxazolidinones; see ref. 28*b*. Comparison of auxiliaries see ref. 28*c*. Others: Oppolzer and Helmchen auxiliary; see ref. 28*d–f*. Addition of aryl Grignards and (or) coppers to oxazolidinone enoates see ref. 28*g*. Addition to 4-phenyl-oxazolidinone derived enoates see ref. 28*h*. For other efforts in the area see ref. 28*i*.

[8] Williams has recently shown that 4-benzyloxazolidinone is a useful chiral auxiliary in conjugate additions using Yamamoto's reagent. See ref. 12*b*.

Table 1. Diastereoselective conjugate additions to enoyloxazolidinones.



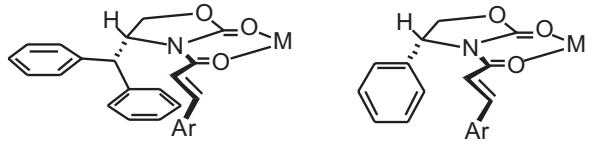
12, 13,14, 24 **25-30**

Entry	Ar	Ar_1	Product	Yield (%)	de (%)
1	3,4-(OCH_2O)-5-MeOPh (**12**)	Ph	**25**	90	94
2	3,4,5-$(MeO)_3$Ph (**13**)	3,4-(OCH_2O)-5-MeOPh	**26**	89	97
3	3,4,5-$(MeO)_3$Ph (**13**)	3,4-(OCH_2O)Ph	**27**	88	95
4	3,4,5-$(MEO)_3$Ph (**13**)	Ph	**28**	90	96
5	3,4-(OCH_2O)Ph (**14**)	Ph	**29**	97	97
6	Ph (**24**)	3,4-(OCH_2O)Ph	**30**	95	92

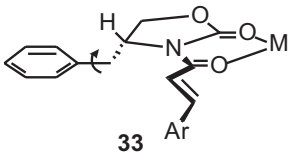
[a]Yields are for purified materials.
[b]des were determined by NMR analysis.

bromobenzene (31) to **13** gave **26**, the intermediate in peperomin analog (**1d**) synthesis, in excellent yield and diastereoselectivity (entry 2). Similarly, intermediate for analog **1e**, was also obtained with high efficiency (entry 3). Conjugate additions to other substrates either varying the nucleophile or the acceptor did not diminish the selectivity (entries 1, 4, 5, and 6). Thus, the 4-diphenylmethyl substituted enoyl oxazolidinones undergo conjugate additions with high selectivity.

The efficient shielding of the β-carbon in conjugate additions by 4-phenyl- and 4-diphenylmethyl-oxazolidinones may suggest that these likely have similar structural organization in the transition states (structures **31** and **32**). In conjugate additions with 4-benzyloxazolidinones (13), the C-4-benzyl bond rotation (**33**) may play a role in the observed low selectivity. The high selectivity observed for organocuprate addition to 4-phenyl and 4-diphenylmethyl derived enoates is in stark contrast to conjugate radical additions where only auxiliary **11** showed high selectivity. Thus, the results depicted in the table and previous work from our laboratory (30) clearly show that the diphenylalanine-derived oxazolidinone can shield the β-carbon effectively in both organocuprate and radical conjugate additions.



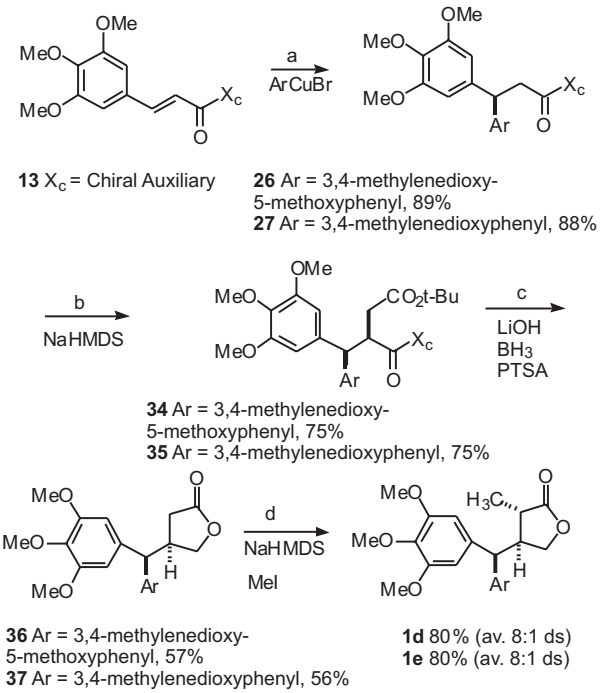
31 M = Lewis acid **32**



33

The basic methodology used in the synthesis of peperomins A, C, and D was adapted for the synthesis of the more complex analogs **1d** and **1e** (Scheme 4). Installation of the two-carbon chain on the conjugate addition products **26** and **27** furnished **34** and **35**. The diastereoselectivity in these alkylations was high with the chiral auxiliary controlling the face selectivity. The succinates were converted to the lactones **36** and **37**, respectively by a hydrolysis–reduction–lactonization sequence. The overall yield for the three steps without purification of the intermediates was excellent. With the lactones at hand, the final installation of the C-3 methyl group was uneventful. As observed in the previous alkylations (vide supra), the diastereoselectivities in these reactions were only moderate (highest ds of 8:1). All attempts at purification of the diastereomeric mixture were not successful. The structural characteristics (^1H and ^{13}C NMR chemical shifts) of analog **1d** are similar to those reported for the natural product peperomin B (1). The structure for the major

Scheme 4.



13 X_c = Chiral Auxiliary

26 Ar = 3,4-methylenedioxy-5-methoxyphenyl, 89%
27 Ar = 3,4-methylenedioxyphenyl, 88%

34 Ar = 3,4-methylenedioxy-5-methoxyphenyl, 75%
35 Ar = 3,4-methylenedioxyphenyl, 75%

36 Ar = 3,4-methylenedioxy-5-methoxyphenyl, 57%
37 Ar = 3,4-methylenedioxyphenyl, 56%

1d 80% (av. 8:1 ds)
1e 80% (av. 8:1 ds)

Key: (a) (i) 3.1 equiv. Mg, (ii) 3.0 equiv. ArBr, (iii) 1.5 equiv. CuBr-$(CH_3)_2S$, -48 to 0°C, 3 h, 3:1 THF-$(CH_3)_2S$; (b) (i)1.1 equiv. NaHMDS, (ii)1.5 equiv. t-BuO_2CCH_2I,-78 to -48°C, 6h , THF; (c) (i) $LiOH/H_2O_2$, (ii) BH_3, (iii) PTSA; (d) (i)1.1 equiv. NaHMDS, (ii)1.5 equiv. CH_3I, 3h, -78°C.

diastereomer (*trans* stereochemistry) of **1d** and **1e** are consistent with the observed ^{1}H NMR coupling constants and spectral similarities to the natural peperomins. The overall yield for **1d** and **1e** were 27 and 26%, respectively.

In conclusion, we have developed a simple and efficient strategy for the synthesis of secolignans peperomin A, C, D, and two analogs. Additionally, we have also shown that 4-diphenylmethyl oxazolidin-2-one (**11**) is an excellent auxiliary in diastereoselective conjugate addition of organocuprates to enoates. The extension of the present methodology for the synthesis of analogs and biological evaluation of the secolignans is currently underway in our laboratory.

Experimental

General experimental details

Methylene chloride (CH_2Cl_2) was distilled from calcium hydride. Tetrahydrofuran (THF), diethyl ether (Et_2O), and benzene were distilled from benzophenone–ketyl prior to use. Methanol (MeOH) was distilled from magnesium turnings and I_2. Acetone was dried from $KMnO_4$ and K_2CO_3. Most of the organic compounds utilized in this study were purchased from Aldrich Chemical Company. All glassware were oven dried, assembled hot, and cooled under a stream of dry nitrogen before use. Reactions with air-sensitive materials were carried out by standard syringe techniques. All reactions were run under an atmosphere of nitrogen unless otherwise noted.

Chromatography and instrumentation

Thin layer chromatographic analyses (TLC) were performed on silica gel Whatmann-60F glass plates and components were visualized by illumination with UV light or by staining with phosphomolybdic acid. Flash column chromatography was performed using E. Merck silica gel 60 (230–400 mesh). ^{1}H NMR was recorded on a 500, 400, or 300 MHz spectrometer. ^{13}C NMR was recorded on 500 (125) MHz, 400 (100) MHz, and 300 (75) MHz spectrometers using broad band proton decoupling. Rotations were recorded on a JASCO-DIP-370 instrument. Elemental analyses were performed on a PerkinElmer Series II CHNS/O analyzer 2400. Melting points was determined using a Fisher–Johns melting point apparatus without correction.

Representative procedure for the acylation of (*R*)-4-diphenylmethyl-2-oxazolidinone (compound 13)

To an oven-dried 100 mL three- neck round- bottomed flask purged with N_2 was added 3.50 g (14.69 mmol) of 3,4,5-trimethoxycinnamic acid. To the solid was added 5 mL (57.23 mmol) of oxalyl chloride dropwise over 2 min and the mixture was allowed to stir at room temperature (rt) for 1 h. Removal of the excess oxalyl chloride under reduced vacuum gave 3.65 g of pure acid chloride (97% yield). To an oven-dried 250 mL three-neck round-bottomed flask purged with N_2 was added 3.0 g (11.86 mmol) of 4-diphenylmethyl-2-oxazolidinone **11** and 40 mL of dry THF. The reaction mixture was cooled to –78°C in an acetone – dry ice bath. To the mixture was added 5.19 mL (12.45 mmol) of *n*-BuLi dropwise over 10 min and the mixture was allowed to stir for 30 min. A solution of 3.35 g (13.05 mmol) of the 3,4,5-trimethoxy cinnamoyl chloride dissolved in 15 mL of dry THF was added dropwise to the solution over 8 min. The solution was stirred at –78°C for 3 h. The reaction was quenched with 10 mL NH_4Cl. The reaction mixture was extracted with ethyl acetate. The combined organics were washed with water followed by brine and dried over $MgSO_4$. Removal of solvent under reduced pressure followed by flash column purification of the crude mixture gave 5.0 g of the acylated product (89% yield).

*(4*R*)-4-(Diphenylmethyl)-3-[3-(3′,4′-methylenedioxy-5′-methoxyphenyl)-2(*E*)-propenoyl]-2-oxazolidinone (**12**)*

Yield: 86%; mp 88–90°C. $[\alpha]_D^{25}$ –192.8 (*c* 0.98, $CHCl_3$). R_f 0.7 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.94 (s, 3H), 4.48 (dd, *J* = 2.7, 8.0 Hz, 2H), 4.81 (d, *J* = 5.4 Hz, 1H), 5.44 (m, 1H), 6.04 (s, 2H), 6.78 (d, *J* = 1.1 Hz, 1H), 6.85 (d, *J* = 1.1 Hz, 1H), 7.22 (m, 10H), 7.70 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 50.6, 56.4, 56.5, 64.7, 102.0, 109.6, 115.1, 127.0, 127.7, 128.3, 128.6, 128.7, 128.8, 129.3, 138.0, 139.6, 143.6, 146.2, 149.2, 153.4, 164.9. Anal. calcd. for $C_{27}H_{23}NO_6$: C 70.89, H 5.07, N 3.06; found: C 70.81, H 5.12, N 2.91.

*(4*R*)-4-(Diphenylmethyl)-3-[3-(3′,4′,5′-trimethoxyphenyl)-2(*E*)-propenoyl]-2-oxazolidinone (**13**)*

Yield: 89%; mp 70 to 71°C. $[\alpha]_D^{25}$ –182.4 (*c* 0.95, $CHCl_3$). R_f 0.5 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.89 (overlapping s, 9H), 4.45 (m, 2H), 4.82 (d, *J* = 5.4 Hz, 1H), 5.44 (m, 1H), 6.82 (s, 2H), 7.22 (m, 10H), 7.75 (d, *J* = 2.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 50.5, 56.1, 56.4, 60.9, 64.8, 105.6, 115.8, 126.9, 127.7, 128.3, 128.6, 128.8, 129.3, 129.9, 138.0, 139.6, 140.4, 146.5, 153.3, 153.5, 164.9. Anal. calcd. for $C_{28}H_{27}NO_6$: C 71.02, H 5.75, N 2.96; found: C 70.94, H 5.76, N 2.84.

*(4*R*)-4-(Diphenylmethyl)-3-[3-(3′,4′-methylenedioxyphenyl)-2(*E*)-propenoyl]-2-oxazolidinone (**14**)*

Yield: 91%; mp 188 to 189°C. $[\alpha]_D^{25}$ –163.3 (*c* 1.0, CH_2Cl_2). R_f 0.56 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.45 (m, 2H), 4.80 (d, *J* = 5.1 Hz, 1H), 5.42 (m, 1H), 6.01 (s, 2H), 6.81 (d, *J* = 8.1 Hz, 1H), 7.22 (m, 12H), 7.70 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 50.7, 56.6, 64.9, 101.8, 107.1, 108.6, 114.8, 125.4, 127.1, 127.9, 128.5, 128.8, 128.9, 129.1, 129.5, 138.3, 139.8, 146.4, 148.4, 150.1, 153.6, 165.2. Anal. calcd. for $C_{26}H_{21}NO_5$: C 73.06, H 4.95, N 3.28; found: C 72.57, H 5.10, N 3.29.

Representative procedure for the conjugate addition — Preparation of 26

To an oven-dried 100 mL round-bottomed flask purged with N_2 was added 1.43 g (58.9 mmol) of magnesium turnings and 10 mL of dry THF. The flask was placed in a ultrasonic bath for 3 min before dropwise addition of 13.18 g (57 mmol) 5-bromo-3-methoxy-1,2-methylenedioxybenzene (dissolved in 24 mL of dry THF) over 20 min. To an oven-dried three-neck 500 mL round-bottomed flask purged with N_2 was added 5.86 g (28.5 mmol) of copper(I) bromide – dimethyl sulfide complex and 40 mL of dimethyl sulfide and 80 mL of dry THF. The reaction mixture was cooled to –48°C in an acetonitrile – dry ice bath. To the mixture was added the Grignard reagent dropwise over 30 min and the mixture was allowed to stir for 30 min. A solution of 9.0 g

(19.0 mmol) of the cinnamate **13** dissolved in 36 mL of dry THF was added dropwise to the solution over 30 min. The solution was stirred at −48°C for 4.5 h. The reaction was quenched with 30 mL NH_4Cl. Excess dimethyl sulfide was removed using a water aspirator. The residue was extracted with ethyl acetate. The combined organics was washed with 10% NH_4OH, water, followed by brine, and dried over $MgSO_4$. Removal of solvent under reduced pressure followed by flash column purification of the crude mixture gave 10.58 g of the addition product **26** (89% yield).

*(4*R*)-4-(Diphenylmethyl)-3-[3-(3,3-bis-3′,4′-methylenedioxy-5′-methoxyphenyl)-propanoyl]-2-oxazolidinone (**15**)*

Yield: 84%; mp 90 to 91°C. $[\alpha]_D^{25}$ –130.8 (*c* 1.0, $CHCl_3$). R_f 0.53 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.55 (m, 2H), 3.87 (two s, 6H), 4.40 (d, *J* = 5.4 Hz, 2H), 4.45 (t, *J* = 7.5, 1H), 4.62 (d, *J* = 4.8 Hz, 1H), 5.24 (m, 1H), 5.93 (m, 4H), 6.46 (m, 4H), 6.90 (s, 2H), 7.03 (d, *J* = 7.0 Hz, 2H), 7.27 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.9, 46.1, 50.3, 56.4, 56.6, 64.8, 101.3, 101.7, 101.8, 107.1, 107.4, 127.0, 127.8, 128.2, 128.6, 128.8, 129.3, 133.7, 133.8, 137.7, 138.1, 138.2, 139.4, 143.4, 143.5, 148.8, 148.9, 153.4, 170.8. Anal. calcd. for $C_{35}H_{31}NO_9$: C 68.96, H 5.03, N 2.30; found: C 68.70, H 4.66, N 2.68.

*(4*R*)-4-(Diphenylmethyl)-3-[3-(3,3-bis-3′,4′,5′-trimethoxyphenyl)-propanoyl]-2-oxazolidinone (**16**)*

Yield: 81%; mp 75 to 76°C. $[\alpha]_D^{25}$ –121.2 (*c* 0.98, $CHCl_3$). R_f 0.43 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.60 (dd, *J* = 7.5, 16.7 Hz, 1H), 3.67 (dd, *J* = 7.5, 16.7 Hz, 1H), 3.82 (three s, 18H), 4.37 (m, 2H), 4.53 (t, *J* = 7.5 Hz, 1H), 4.60 (d, *J* = 4.8 Hz, 1H), 5.22 (m, 1H), 6.51 (s, 2H), 6.56 (s, 2H), 6.85 (m, 2H), 7.02 (d, *J* = 7.5 Hz, 2H), 7.26 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.6, 47.1, 50.3, 56.1, 56.4, 60.8, 64.7, 104.7, 104.9, 127.0, 127.8, 128.1, 128.6, 128.8, 129.2, 136.6, 136.7, 137.7, 138.8, 138.9, 139.4, 153.1, 153.4, 171.0. Anal. calcd. for $C_{37}H_{39}NO_9$: C 69.25, H 6.13, N 2.18; found: C 69.15, H 6.19, N 2.01.

*(4*R*)-4-(Diphenylmethyl)-3-[3-(3,3-bis-3′,4′-methylenedioxyphenyl)-propanoyl]-2-oxazolidinone (**17**)*

Yield: 89%; mp 86 to 87°C. $[\alpha]_D^{25}$ –112.7 (*c* 1.03, CH_2Cl_2). R_f 0.50 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.51 (dd, *J* = 7.5, 17.4 Hz, 1H), 3.58 (dd, *J* = 7.5, 17.4 Hz, 1H), 4.38 (d, *J* = 4.8 Hz, 2H), 4.46 (t, *J* = 7.8 Hz, 1H), 4.61 (d, *J* = 5.1 Hz, 1H), 5.23 (m, 1H), 5.89 (s, 2H), 5.92 (s, 2H), 6.73 (m, 6H), 6.92 (d, *J* = 3.2 Hz, 2H), 7.03 (d, *J* = 6.7 Hz, 2H), 7.27 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 41.2, 45.5, 50.4, 56.4, 64.9, 101.1, 108.3, 108.4, 120.5, 120.8, 127.1, 127.9, 128.3, 128.7, 128.9, 129.4, 137.7, 137.9, 139.5, 146.2, 146.3, 147.8, 147.9, 153.5, 170.9. Anal. calcd. for $C_{33}H_{27}NO_7$: C 72.12, H 4.95, N 2.55; found: C 71.64, H 5.00, N 2.54.

*(3(3*S*),4*R*)-4-(Diphenylmethyl)-3-[3-(3,3-(phenyl)-(3″,4″-methylenedioxy-5″-methoxyphenyl)-propanoyl]-2-oxazolidinone (**25**)*

Yield: 90%; mp 146–148°C. $[\alpha]_D^{25}$ –140.0 (*c* 0.69, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.59 (dd, *J* = 17.3, 7.1 Hz, 1H), 3.70 (dd, *J* = 17.3, 8.1 Hz, 1H), 3.89 (s, 3H), 4.38 (m, 2H), 4.57 (t, *J* = 7.5 Hz, 1H), 4.63 (d, *J* = 5.0 Hz, 1H), 5.24 (m, 1H), 5.93 (m, 2H), 6.53 (s, 2H), 6.91 (m, 2H), 7.05 (m, 2H), 7.25 (m, 11H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 41.1, 46.5, 50.5, 56.6, 56.9, 65.0, 101.6, 102.3, 107.8, 126.9, 127.3, 127.8, 128.1, 128.5, 128.9, 134.1, 138.0, 138.6, 139.7, 143.8, 149.2, 153.7, 171.3. Anal. calcd. for $C_{33}H_{29}NO_6$: C 74.00, H 5.46, N 2.62; found: C 73.74, H 5.33, N 2.73.

*(3(3*S*),4*R*)-4-(Diphenylmethyl)-3-[3-(3,3-(3′,4′,5′-trimethoxyphenyl)-(3″,4″-methylenedioxy-5″-methoxyphenyl)-propanoyl]-2-oxazolidinone (**26**)*

Yield: 89%; mp 88 to 89°C. $[\alpha]_D^{25}$ –95.1 (c 1.0, CH_2Cl_2). R_f 0.42 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.53 (dd, *J* = 7.5, 17.2 Hz, 1H), 3.66 (dd, *J* = 7.5, 16.9 Hz, 1H), 3.81 (s, 3H), 3.84 (s, 6H), 3.87 (s, 3H), 4.39 (d, *J* = 5.1 Hz, 2H), 4.49 (t, *J* = 7.2 Hz, 1H), 4.60 (d, *J* = 5.4 Hz, 1H), 5.23 (m, 1H), 5.92 (s, 2H), 6.46 (s, 2H), 6.52 (s, 2H), 6.82 (d, *J* = 5.6 Hz, 2H), 7.01 (d, *J* = 6.7 Hz, 2H), 7.26 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.9, 46.7, 50.4, 56.3, 56.6, 56.8, 60.9, 64.8, 101.4, 101.8, 104.9, 107.4, 127.1, 128.0, 128.3, 128.7, 128.9, 129.3, 133.9, 136.7, 137.8, 138.2, 139.2, 139.6, 143.5, 149.0, 153.3, 153.6, 171.1. Anal. calcd. for $C_{36}H_{35}NO_9$: C 69.11, H 5.64, N 2.24; found: C 69.49, H 5.79, N 2.04.

*(3(3*S*),4*R*)-4-(Diphenylmethyl)-3-[3-(3,3-(3′,4′,5′-trimethoxyphenyl)-(3″,4″-methylenedioxyphenyl)-propanoyl]-2-oxazolidinone (**27**)*

Yield: 88%; mp 84 to 85°C. $[\alpha]_D^{25}$ –105.2 (*c* 1.0, CH_2Cl_2). R_f 0.42 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.50 (dd, *J* = 7.5, 17.2 Hz, 1H), 3.70 (dd, *J* = 7.8, 17.2 Hz, 1H), 3.81 (s, 3H), 3.84 (s, 6H), 4.39 (d, *J* = 4.8 Hz, 2H), 4.51 (t, *J* = 7.2 Hz, 1H), 4.60 (d, *J* = 5.1 Hz, 1H), 5.23 (m, 1H), 5.91 (s, 2H), 6.52 (s, 2H), 6.74 (m, 3H), 6.82 (d, *J* = 5.9 Hz, 2H), 7.01 (d, *J* = 7.2 Hz, 2H), 7.24 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.9, 46.4, 50.3, 56.2, 56.6, 60.9, 64.8, 101.1, 104.9, 108.3, 120.4, 127.1, 127.9, 128.3, 128.4, 128.7, 128.9, 129.3, 136.6, 137.5, 137.8, 139.4, 139.6, 146.3, 147.9, 153.3, 153.5, 171.1. Anal. calcd. for $C_{35}H_{33}NO_8$: C 70.58, H 5.58, N 2.35; found: C 70.57, H 5.86, N 1.92.

*(3(3*S*),4*R*)-4-(Diphenylmethyl)-3-[3-(3,3-(phenyl)-(3′,4′,5′-trimethoxyphenyl)-propanoyl]-2-oxazolidinone (**28**)*

Yield: 90%; mp 125–127°C. $[\alpha]_D^{25}$ –131.2 (*c* 0.42, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.61 (dd, *J* = 17.0, 7.1 Hz, 1H), 3.82 (dd, *J* = 17.0, 8.2 Hz, 1H), 3.85 (s, 3H), 3.88 (s, 6H), 4.41 (m, 2H), 4.65 (m, 2H), 5.25 (m, 1H), 6.59 (s, 2H), 6.85 (m, 2H), 7.27 (m, 13H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 40.9, 47.0, 50.5, 56.4, 56.7, 61.1, 65.0, 105.3, 126.9, 127.3, 127.9, 128.1, 128.4, 128.9, 129.1, 129.5, 136.8, 138.0, 139.5, 140.0, 143.7, 153.5, 171.4. Anal. calcd. for $C_{34}H_{33}NO_6$: C 74.03, H 6.03, N 2.54; found: C 74.01, H 5.95, N 2.53.

*(3(3*S*),4*R*)-4-(Diphenylmethyl)-3-[3-(3,3-(3′,4′-methylenedioxyphenyl)-(phenyl)-propanoyl]-2-oxazolidinone (**29**)*

Yield: 97%; mp 164–166°C. $[\alpha]_D^{25}$ –142.5 (*c* 0.56, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.60 (dd, *J* = 17.5, 7.5 Hz, 1H), 3.67 (dd, *J* = 17.5, 7.4 Hz, 1H), 4.37 (m, 2H), 4.57 (t, *J* = 7.6 Hz, 1H), 4.63 (d, *J* = 5.2 Hz, 1H), 5.23 (m,

1H), 5.92 (m, 2H), 6.77 (m, 3H), 6.93 (m, 2H), 7.05 (m, 2H), 7.26 (m, 11H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 41.2, 46.0, 50.5, 56.6, 65.0, 101.2, 108.5, 108.8, 121.2, 126.8, 127.3, 127.9, 128.1, 128.5, 128.9, 129.1, 129.6, 137.9, 138.0, 139.7, 143.9, 146.4, 148.0, 153.7, 171.2. Anal. calcd. for $C_{32}H_{27}NO_5$: C 76.02, H 5.38, N 2.77; found: C 76.14, H 5.41, N 2.66.

*(3(3*R*),4*R*)-4-(Diphenylmethyl)-3-[3-(3,3-(3′,4′-methylenedioxyphenyl)-(phenyl)-propanoyl]-2-oxazolidinone (**30**)*

Yield: 95%; mp 78–81°C. $[\alpha]_D^{25}$ –142.2 (*c* 0.49, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.57 (dd, *J* = 17.6, 7.3 Hz, 1H), 3.69 (dd, *J* = 17.8, 7.8 Hz, 1H), 4.38 (m, 2H), 4.57 (t, *J* = 7.5 Hz, 1H), 4.63 (d, *J* = 5.2 Hz, 1H), 5.25 (m, 1H), 5.90 (s, 2H), 6.76 (m, 3H), 6.92 (m, 2H), 7.05 (m, 2H), 7.27 (m, 11H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 41.3, 46.0, 50.5, 56.6, 65.1, 101.2, 108.5, 108.7, 120.9, 126.9, 127.3, 127.9, 128.1, 128.5, 128.9, 129.1, 129.6, 137.9, 138.0, 139.7, 144.1, 146.3, 148.0, 153.7, 171.3. Anal. calcd. for $C_{32}H_{27}NO_5$: C 76.02, H 5.38, N 2.77; found: C 76.20, H 5.32, N 2.87.

Representative procedure for alkylation (compound 34)

To an oven-dried 250 mL three- neck round-bottomed flask purged with N_2 was added 10.5 g (16.78 mmol) of **26** and 120 mL of dry THF. The reaction mixture was cooled to –78°C in an acetone –dry ice bath. To the mixture was added 18.46 mL (18.46 mmol) of a 1 M NaHMDS–THF solution dropwise over 20 min and the mixture was allowed to stir for 1 h. To the solution was added 2.92 mL (20.14 mmol) of *tert*-butyl iodoacetate dropwise over 6 min. The solution was stirred at –78°C for 6 h. The reaction was quenched with 20 mL NH_4Cl. The reaction mixture was extracted with ethyl acetate. The combined organics were washed with water, followed by brine, and dried over $MgSO_4$. Removal of solvent under reduced pressure followed by flash column purification of the crude mixture led to 9.3 g of the alkylated product **34** (75% yield).

*(3(2*S*),4*R*)-4-(Diphenylmethyl)-3-[bis-(3′,4′-methylenedioxy-5′-methoxyphenyl)-methyl]-(4-oxo-butyric acid* tert*-butyl ester)-2-oxazolidinone (**18**)*

Yield: 64%; mp 189 to 190°C. $[\alpha]_D^{25}$ –289.9 (*c* 1.09, $CHCl_3$). R_f 0.63 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48 (s, 9H), 2.48 (dd, *J* = 3.2, 17.2 Hz, 1H), 2.82 (dd, *J* = 10.8, 17.2 Hz, 1H), 3.77 (m, 2H), 3.83 (s, 3H), 3.90 (s, 3H), 4.22 (d, *J* = 8.6 Hz, 1H), 4.70 (m, 2H), 5.17 (ddd, *J* = 3.2, 3.8, 10.8 Hz, 1H), 5.93 (m, 4H), 6.42 (d, *J* = 5.9 Hz, 2H), 6.51 (s, 1H), 6.62 (s, 1H), 6.99 (d, *J* = 7.5 Hz, 2H), 7.28 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.1, 37.3, 42.9, 50.1, 55.6, 56.3, 56.6, 56.9, 63.9, 80.9, 101.3, 101.4, 101.8, 102.4, 106.9, 107.7, 126.8, 127.5, 128.0, 128.4, 128.6, 129.6, 133.8, 134.2, 135.1, 135.8, 137.9, 140.0, 143.1, 143.6, 148.3, 149.2, 170.9, 174.8. Anal. calcd. for $C_{41}H_{41}NO_{11}$: C 68.04, H 5.71, N 1.94; found: C 68.03, H 5.73, N 1.73.

*(3(2*S*),4*R*)-4-(Diphenylmethyl)-3-[bis-(3′,4′,5′-trimethoxyphenyl)-methyl]-(4-oxo-butyric acid* tert*-butyl ester)-2-oxazolidinone (**19**)*

Yield: 66%; mp 90 to 91°C. $[\alpha]_D^{25}$ –265.4 (*c* 0.95, CH_2Cl_2). R_f 0.33 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.46 (s, 9H), 2.46 (dd, *J* = 3.5, 16.9 Hz, 1H), 2.87 (dd, *J* = 10.9, 16.9 Hz, 1H), 3.61 (t, *J* = 8.5 Hz, 1H), 3.76 (s, 3H), 3.79 (s, 6H), 3.80 (d, *J* = 11 Hz, 1H), 3.82 (s, 3H), 3.87 (s, 6H), 4.12 (dd, *J* = 1.8, 7.3 Hz, 1H), 4.52 (dd, *J* = 2.4, 8.2 Hz, 1H), 4.65 (d, *J* = 2.5 Hz, 1H), 5.26 (ddd, *J* = 3.2, 3.5, 11.0 Hz, 1H), 6.48 (s, 2H), 6.64 (s, 2H), 6.93 (d, *J* = 6.9 Hz, 2H), 7.25 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.3, 37.7, 43.3, 50.1, 56.1, 56.3, 56.9, 57.2, 60.8, 60.9, 63.9, 81.1, 105.0, 126.9, 127.7, 128.1, 128.5, 128.8, 129.8, 136.3, 136.6, 137.2, 137.9, 140.2, 152.8, 153.3, 153.6, 171.3, 175.2. Anal. calcd. for $C_{43}H_{49}NO_{11}$: C 68.33, H 6.53, N 1.85; found: C 67.97, H 6.45, N 1.76.

*(3(2*S*),4*R*)-4-(Diphenylmethyl)-3-[bis-(3′,4′-methylenedioxyphenyl)-methyl]-(4-oxo-butyric acid* tert*-butyl ester)-2-oxazolidinone (**20**)*

Yield: 74%; mp 104 to 105°C. $[\alpha]_D^{25}$ –252.3 (*c* 0.55, $CHCl_3$). R_f 0.62 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 (s, 9H), 2.50 (dd, *J* = 3.2, 17.2 Hz, 1H), 2.82 (dd, *J* = 10.8, 17.2 Hz, 1H), 3.69 (t, *J* = 8.9 Hz, 1H), 3.85 (d, *J* = 11.3 Hz, 1H), 4.19 (d, *J* = 8.8 Hz, 1H), 4.69 (s, 2H), 5.18 (ddd, *J* = 3.2, 3.2, 11.0 Hz, 1H), 5.85 (m, 2H), 5.93 (s, 2H), 6.77 (m, 6H), 7.00 (d, *J* = 8.3 Hz, 2H), 7.28 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.3, 37.4, 43.1, 50.2, 55.0, 57.0, 64.0, 81.0, 101.1, 107.8, 108.5, 108.7, 108.8, 121.3, 127.0, 127.6, 128.2, 128.4, 128.6, 128.8, 130.0, 134.6, 135.5, 138.1, 140.3, 146.4, 146.6, 147.5, 148.2, 152.9, 171.2, 175.1. Anal. calcd. for $C_{39}H_{37}NO_9$: C 70.58, H 5.62, N 2.11; found: C 70.29, H 5.60, N 1.96.

*(3(2*S*),3(3*S*),4*R*)-4-(Diphenylmethyl)-3-[(3′,4′,5′-trimethoxyphenyl)-(3″,4″-methylenedioxy-5″-methoxyphenyl)-methyl]-(4-oxo-butyric acid* tert*-butyl ester)-2-oxazolidinone (**34**)*

Yield: 75%; mp 231 to 232°C. $[\alpha]_D^{25}$ –251.4 (*c* 1.0, CH_2Cl_2). R_f 0.46 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.46 (s, 9H), 2.46 (dd, *J* = 3.2, 16.7 Hz, 1H), 2.82 (dd, *J* = 10.8, 16.9 Hz, 1H), 3.72 (t, *J* = 9.1 Hz, 1H), 3.81 (s, 3H), 3.82 (s, 3H), 3.83 (d, *J* = 11.3 Hz, 1H) 3.86 (s, 6H), 4.20 (d, *J* = 7.6 Hz, 1H), 4.68 (d, *J* = 3.5 Hz, 2H), 5.23 (m, 1H), 5.88 (m, 2H), 6.44 (d, *J* = 10.2 Hz, 2H), 6.57 (s, 2H), 6.98 (d, *J* = 7.3 Hz, 2H), 7.26 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.3, 37.6, 43.1, 50.2, 56.2, 56.4, 57.1, 60.9, 64.1, 81.1, 101.6, 102.6, 104.9, 107.2, 127.0, 127.7, 128.2, 128.6, 128.8, 129.8, 134.0, 135.8, 136.4, 137.1, 138.0, 140.2, 143.2, 148.5, 153.1, 153.6, 171.2, 175.0. Anal. calcd. for $C_{42}H_{45}NO_{11}$: C 68.19, H 6.13, N 1.89; found: C 67.94, H 6.09, N 1.92.

*(3(2*S*),3(3*S*),4*R*)-4-(Diphenylmethyl)-3-[(3′,4′,5′-trimethoxyphenyl)-(3″,4″-methylenedioxyphenyl)-methyl]-(4-oxo-butyric acid* tert*-butyl ester)-2-oxazolidinone (**35**)*

Yield: 75%; mp 214 to 215°C. $[\alpha]_D^{25}$ –261.8 (*c* 1.0, CH_2Cl_2). R_f 0.55 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 (s, 9H), 2.46 (dd, *J* = 3.2, 16.9 Hz, 1H), 2.83 (dd, *J* = 11.0, 17.0 Hz, 1H), 3.62 (t, *J* = 8.3 Hz, 1H), 3.76 (s, 3H), 3.79 (s, 6H), 3.79 (d, *J* = 11.3 Hz, 1H), 4.12 (dd, *J* = 1.9, 8.9 Hz, 1H), 4.53 (dd, *J* = 2.7, 5.9 Hz, 1H), 4.66 (d, *J* = 2.7 Hz, 1H), 5.23 (ddd, *J* = 3.0, 3.5, 11.6 Hz, 1H), 5.94 (s, 2H), 6.42 (s, 2H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.92 (m, 4H), 7.25 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.3, 37.6, 43.0, 50.1, 56.1, 57.2, 60.8,

63.9, 81.0, 101.3, 104.9, 108.4, 108.7, 121.1, 126.9, 127.6, 128.1, 128.5, 128.8, 129.8, 134.5, 136.4, 137.1, 138.0, 140.2, 146.8, 148.2, 152.9, 153.2, 171.2, 175.2. Anal. calcd. for $C_{41}H_{43}NO_{10}$: C 69.38, H 6.11, N 1.97; found: C 69.17, H 6.17, N 1.99.

General procedure for the LAH reduction–cyclization (compounds 21 and 22)

To an oven-dried 25 mL two-neck round-bottomed flask purged with N_2 was added 1.00 g of **18** (1.38 mmol) of alkylated product and 2 mL of dry THF. The reaction mixture was cooled to –78°C in an acetone – dry ice bath. To the solution was added 265 mg (6.99 mmol) of LAH in 7 mL of dry THF dropwise over 15 min. The reaction was stirred at –78°C for 20 h before quenching with ethyl acetate. The mixture was filtered through Celite and dried over $MgSO_4$. Removal of solvent under reduced pressure led to the crude alcohol. The crude alcohol cyclized on standing and (or) during column chromatography over silica gel. Lactone (410 mg) was obtained after column chromatography (74% yield for **21**).

General procedure for hydrolysis–reduction–cyclization (for compounds 23, 36, 37)

To an oven-dried 250 mL three-neck round-bottomed flask purged with N_2 was added 3.00 g (4.05 mmol) of alkylated product **34**, 60 mL of THF, and 15 mL of H_2O. The reaction mixture was cooled to 0°C before the dropwise addition of 3.31 mL (32.4 mmol) of 30% H_2O_2 over 10 min. To the solution was added 747 mg (17.82 mmol) of LiOH–H_2O in 15 mL of H_2O dropwise over 20 min. The reaction was stirred at 0°C for 5 h before being allowed to warm to room temperature and stirred for 14 h. The reaction was cooled to 0°C before quenching with 4.20 g of Na_2SO_3 in 20 mL of H_2O. The mixture was washed with H_2O and extracted with CH_2Cl_2. The aqueous layer was acidified to pH = 2 with 5 M HCl before extraction with ethyl acetate. The organic extracts were not combined and both were dried over $MgSO_4$. Removal of solvent from the acid wash under reduced pressure led to 1.75 g of crude acid (86% yield). Evaporation of the neutral fraction provided crude chiral auxiliary.

General procedure for the borane reduction

To an oven-dried 100 mL three-neck round-bottomed flask purged with N_2 was added 1.90 g (3.77 mmol) of crude acid and 50 mL of dry THF. The reaction mixture was cooled to –10°C in an acetone – ice bath. To the solution was added 7.54 mL (7.54 mmol) of a 1 M BH_3–THF solution dropwise over 15 min. The reaction was stirred at –10°C for 6 h before warming to room temperature and stirred for 14 h. The reaction was quenched with 4 mL of a 1:1 solution of acetic acid and water. The aqueous layer was washed with a cold saturated solution of $NaHCO_3$ and extracted with ethyl acetate while being dried over $MgSO_4$. Removal of solvent under reduced pressure led to 1.43 g of crude alcohol (75% yield).

Lactonization

To an oven-dried 50 mL two-neck round- bottomed flask set up with a condenser purged with N_2 was added 1.60 g (3.26 mmol) of crude alcohol, 15 mg of PTSA, and 30 mL of benzene. The solution was heated to reflux for 2.0 h before being allowed to cool to room temperature. The mixture was washed with $NaHCO_3$ and water before extracting with ethyl acetate and drying over $MgSO_4$. Removal of solvent under reduced pressure followed by flash column purification of the crude mixture led to 1.2 g of the lactone **36** (89% yield).

*(4S)-4-[1-Bis(3′,4′-methylenedioxy-5′-methoxyphenyl)methyl]-butyrolactone (**21**)*

Overall yield over two steps: 74% (average of three runs); mp 147 to 148°C. $[\alpha]_D^{25}$ –9.2 (*c* 0.59, CH_2Cl_2). R_f 0.4 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.26 (dd, *J* = 7.5, 10.2 Hz, 1H), 2.59 (dd, *J* = 8.3, 9.4 Hz, 1H), 3.24 (m, 1H), 3.57 (d, *J* = 11.8 Hz, 1H), 3.89 (s, 6H), 3.96 (dd, *J* = 6.4, 9.4 Hz, 1H), 4.28 (dd, *J* = 7.2, 9.4 Hz, 1H), 5.92 (two s, 4H), 6.39 (two s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.1, 40.1, 55.3, 57.0, 72.0, 101.1, 101.6, 107.7, 134.3, 136.4, 136.8, 143.7, 149.5, 176.5. Anal. calcd. for $C_{21}H_{20}O_8$: C 63.00, H 5.03; found: C 63.34, H 5.05.

*(4S)-4-[1-Bis(3′,4′,5′-trimethoxyphenyl)methyl]-butyrolactone (**22**)*

Overall yield over two steps: 75% (average of three runs); mp 168 to 169°C. $[\alpha]_D^{25}$ –13.0 (*c* 1.0, $CHCl_3$). R_f 0.16 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.26 (dd, *J* = 7.5, 17.8 Hz, 1H), 2.59 (dd, *J* = 8.0, 18.0 Hz, 1H), 3.32 (m, 1H), 3.64 (d, *J* = 11.8 Hz, 1H), 3.80 (s, 6H), 3.84 (s, 12H), 3.98 (dd, *J* = 6.7, 9.4 Hz, 1H), 4.27 (dd, *J* = 7.2, 9.4 Hz, 1H), 6.45 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.9, 38.1, 53.7, 54.2, 58.8, 70.0, 102.7, 135.5, 135.9, 151.8, 174.9. Anal. calcd. for $C_{23}H_{28}O_8$: C 63.88, H 6.53; found: C 63.56, H 6.30.

*(4S)-4-[1-Bis(3′,4′-methylenedioxyphenyl)methyl]-butyrolactone (**23**)*

Overall yield over three steps: 56% (average of three runs); mp 66 to 67°C. $[\alpha]_D^{25}$ –4.3 (*c* 1.0, CH_2Cl_2). R_f 0.44 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.24 (dd, *J* = 8.1, 18.0 Hz, 1H), 2.56 (dd, *J* = 8.6, 18.0 Hz, 1H), 3.27 (m, 1H), 3.64 (d, *J* = 11.6 Hz, 1H), 3.94 (dd, *J* = 7.0, 9.4, 1H), 4.25 (dd, *J* = 7.5, 9.4 Hz, 1H), 5.90 (two s, 4H), 6.70 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.1, 34.1, 40.0, 54.8, 72.2, 101.2, 107.7, 108.6, 120.5, 120.6, 128.4, 135.9, 136.4, 146.6, 146.7, 148.2,176.7. Anal. calcd. for $C_{19}H_{16}O_6$: C 67.06, H 4.74; found: C 67.25, H 4.96.

*(4(1S),4S)-4-[1,1-(3′,4′,5′-Methoxyphenyl)-(3″,4″-methylenedioxy-5″-methoxyphenyl)methyl]-butyrolactone (**36**)*

Overall yield over three steps: 57% (average of three runs); mp 77 to 78°C. $[\alpha]_D^{25}$ –12.8 (*c* 0.9, CH_2Cl_2). R_f 0.20 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.26 (dd, *J* = 7.5, 17.7 Hz, 1H), 2.59 (dd, *J* = 8.0, 17.7 Hz, 1H), 3.29 (m, 1H), 3.61 (d, *J* = 11.8 Hz, 1H), 3.80 (s, 3H), 3.84 (s, 6H), 3.90 (s, 3H), 3.98 (dd, *J* = 6.4, 9.4 Hz, 1H), 4.28 (dd, *J* = 7.0, 9.4 Hz, 1H), 5.93 (d, *J* = 2.7 Hz, 2H), 6.41 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.4, 34.1, 40.1, 55.5, 56.3, 57.0, 60.9, 72.1, 101.1, 101.6, 104.5, 107.8, 134.3, 136.4, 137.1, 137.9, 143.7, 149.5, 153.5, 176.6. Anal. calcd. for $C_{22}H_{24}O_8$: C 63.45, H 5.81; found: C 63.39, H 6.04.

*(4(1S),4S)-4-[1,1-(3′,4′,5′-Methoxyphenyl)-5-(3″,4″-methylenedioxyphenyl)methyl]-butyrolactone (**37**)*

Overall yield over three steps: 56% (average of three runs); mp 69 to 70°C. $[\alpha]_D^{25}$ –4.6 (*c* 1.0, CH_2Cl_2). R_f 0.26 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (dd, *J* = 8.6, 17.7 Hz, 1H), 2.56 (dd, *J* = 9.1, 17.7 Hz, 1H), 3.30 (m, 1H), 3.64 (d, *J* = 11.6 Hz, 1H), 3.78 (s, 3H), 3.82 (s, 6H), 3.94 (dd, *J* = 7.0, 16.4 Hz, 1H), 4.25 (dd, *J* = 9.4, 19.1 Hz, 1H), 5.90 (m, 2H), 6.41 (s, 2H), 6.71 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.1, 40.0, 55.3, 56.3, 60.9, 72.1, 101.3, 104.4, 107.7, 108.6, 120.5, 128.4, 135.6, 136.1, 137.0, 137.7, 138.1, 146.8, 148.2, 153.5, 176.6. Anal. calcd. for $C_{21}H_{22}O_7$: C 65.28, H 5.74; found: C 64.81, H 5.46.

Representative methylation procedure (compound 1d)

To an oven-dried 25 mL two-neck round-bottomed flask purged with N_2 was added 400 mg (0.961 mmol) of the lactone **36** and 7 mL of dry THF. The reaction mixture was cooled to –78°C in an acetone – dry ice bath. To the mixture was added 1.15 mL (1.15 mmol) of a 1 M NaHMDS–THF solution dropwise over 3 min and the mixture was allowed to stir for 50 min. To the solution was added 0.12 mL (1.92 mmol) of methyl iodide over 1 min. The solution was stirred at –78°C for 5 h. The reaction was quenched with 1 mL NH_4Cl. The reaction mixture was extracted with ethyl acetate. The combined organics were washed with water, followed by brine, and dried over $MgSO_4$. Removal of solvent under reduced pressure followed by flash column purification of the crude mixture led to 331 mg of the natural product peperomin B (**1d**) along with the diastereomer (80% yield).

*(3S,4S)-3-Methyl-4-[1-bis(3′,4′-methylenedioxy-5′-methoxyphenyl)methyl]-butyrolactone (peperomin A (**1a**))*

Yield: 98%; mp 143 to 144°C (abs. EtOH) (lit. (1) 143–145°C). $[\alpha]_D^{25}$ 22.7 (*c* 0.13, $CHCl_3$) (lit. (1) $[\alpha]_D^{27}$ 20.6 (*c* 0.14, $CHCl_3$)). R_f 0.5 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.94 (d, *J* = 7.2 Hz, 3H), 2.34 (m, 1H), 2.84 (m, 1H), 3.57 (d, *J* = 11.3 Hz, 1H), 3.80 (dd, *J* = 7.8, 9.7 Hz, 1H), 3.89 (s, 6H), 4.30 (dd, *J* = 7.5, 9.6 Hz, 1H), 5.93 (s, 4H), 6.38–6.44 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.9, 40.3, 47.3, 56.2, 57.0, 70.4, 101.2, 101.4, 101.6, 107.7, 134.3, 136.2, 136.8, 143.6, 149.4, 179.7. Anal. calcd. for $C_{22}H_{22}O_8$: C 63.76, H 5.35; found: C 63.84, H 5.22.

*(3S,4S)-3-Methyl-4-[1-bis(3′,4′,5′-trimethoxyphenyl)methyl]-butyrolactone (peperomin C (**1b**))*

Yield: 98%; mp 156 to 157°C (EtOAC–hexane), (lit. (1) 158–160°C). $[\alpha]_D^{25}$ 43.3 (*c* 0.06, $CHCl_3$) (lit. (1) $[\alpha]_D^{27}$ 42.7 (*c* 0.06, $CHCl_3$)). R_f 0.22 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.94 (d, *J* = 7.2 Hz, 3H), 2.37 (m, 1H), 2.92 (m, 1H), 3.64 (d, *J* = 11.3 Hz, 1H), 3.81 (s, 6H), 3.83 (m, 1H), 3.84 (s, 6H), 3.86 (s, 6H), 4.30 (dd, *J* = 7.8, 9.7 Hz, 1H), 6.48 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.9, 40.4, 47.5, 56.3, 56.7, 61.0, 70.5, 104.7, 104.9, 137.2, 137.4, 137.6, 153.6, 179.7. Anal. calcd. for $C_{24}H_{30}O_8$: C 64.56, H 6.77; found: C 64.29, H 6.40.

*(3S,4S)-3-Methyl-4-[1-bis(3′,4′-methylenedioxyphenyl)methyl]-butyrolactone (peperomin D (**1c**))*

Yield: 80%; mp 120–122°C (lit. (2) 122–124°C). $[\alpha]_D^{25}$ 18.4 (*c* 0.13, $CHCl_3$) (lit. (2) $[\alpha]_D^{27}$ 23.0 (*c* 0.1, $CHCl_3$)). R_f 0.50 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (d, *J* = 7.3 Hz, 3H), 2.33 (m, 1H), 2.87 (m, 1H), 3.63 (d, *J* = 11.2 Hz, 1H), 3.76 (dd, *J* = 8.2, 9.4 Hz, 1H), 4.28 (dd, *J* = 7.6, 9.4 Hz, 1H), 5.90 (s, 4H), 6.70 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.8, 40.4, 47.3, 55.7, 70.5, 101.2, 107.7, 107.8, 108.6, 108.7, 120.4, 120.8, 135.7, 136.3, 146.7, 148.2, 148.3, 179.8. Anal. calcd. for $C_{20}H_{18}O_6$: C 67.68, H 5.12; found: C 67.21, H 5.08.

*(3S,4S,5R)-3-Methyl-4-[1,1-(3′,4′,5′-methoxyphenyl)-5-(3″,4″-methylenedioxy-5″-methoxyphenyl)methyl]-butyrolactone (peperomin analog (**1d**))*

The minor diastereomer could not be separated. Chemical shifts for the major compound are reported. Yield: 80%; mp 84 to 85°C. $[\alpha]_D^{25}$ 13.9 (*c* 0.49, $CHCl_3$). R_f 0.26 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (d, *J* = 7.3 Hz, 3H), 2.35 (m, 1H), 2.90 (m, 1H), 3.61 (d, *J* = 11.3 Hz, 1H), 3.80 (s, 3H), 3.80 (overlapping with OMe peaks, dd, 1H) 3.84 (s, 6H), 3.90 (s, 3H), 4.30 (dd, *J* = 7.6, 9.7 Hz, 1H), 5.94 (s, 2H), 6.41 (d, *J* = 1.6 Hz, 1H), 6.44 (s, 2H), 6.48 (d, *J* = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.0, 40.3, 47.3, 56.3, 56.4, 57.1, 61.0, 70.4, 101.2, 101.6, 104.7, 107.9, 128.4, 134.4, 136.2, 137.3, 137.7, 143.7, 149.5, 153.6, 179.7. Anal. calcd. for $C_{23}H_{26}O_8$: C 64.18, H 6.01; found: C 64.14, H 5.55.

*(3S,4S,5R)-3-Methyl-4-[1,1-(3′,4′,5′-methoxyphenyl)-5-(3″,4″-methylenedioxyphenyl)methyl]-butyrolactone (peperomin analog (**1e**))*

The minor diastereomer could not be separated. Chemical shifts for the major compound are reported. Yield: 80%; mp 181 to 182°C. $[\alpha]_D^{25}$ 35.3 (*c* 0.17, $CHCl_3$). R_f 0.34 (50:50, EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (d, *J* = 7.2 Hz, 3H), 2.35 (m, 1H), 2.90 (m, 1H), 3.63 (d, *J* = 11.3 Hz, 1H), 3.79 (s, 3H), 3.80 (overlapping with OMe peaks, dd, 1H), 3.83 (s, 6H), 4.28 (dd, *J* = 7.6, 9.6 Hz, 1H), 5.92 (s, 2H), 6.43 (s, 2H), 6.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.9, 40.4, 47.2, 56.2, 56.3, 60.9, 70.4, 101.3, 104.7, 107.8, 108.7, 120.5, 135.5, 137.2, 137.9, 146.8, 148.3, 153.5, 179.8. Anal. calcd. for $C_{22}H_{24}O_7$: C 65.99, H 6.04; found: C 65.92, H 5.86.

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