รายงานวิจัยฉบับสมบูรณ์

โครงการ การสังเคราะห์สารประเภทเซโคลิกแนนที่สกัดได้จากพืชสมุนไพรไทยที่มีฤทธิ์ทางชีวภาพ

โดย ผู้ช่วยศาสตราจารย์ ดร. ดรุณี สู้รักรัมย์ และคณะ

ตุลาคม พ.ศ. 2557

สัญญาเลขที่ MRG5580046

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	คณะผู้วิจัย	สังกัด
นักวิจัยผู้รับทุน	ผู้ช่วยศาสตราจารย์ ดร. ดรุณี สู้รักรัมย์	ภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยมหิดล
นักวิจัยที่ปรึกษา	1. ศาสตราจารย์ ดร. มนัส พรหมโคตร	ภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยมหิดล
	2. ศาสตราจารย์ ดร. ปทุมรัตน์ ตู้จินดา	ภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยมหิดล

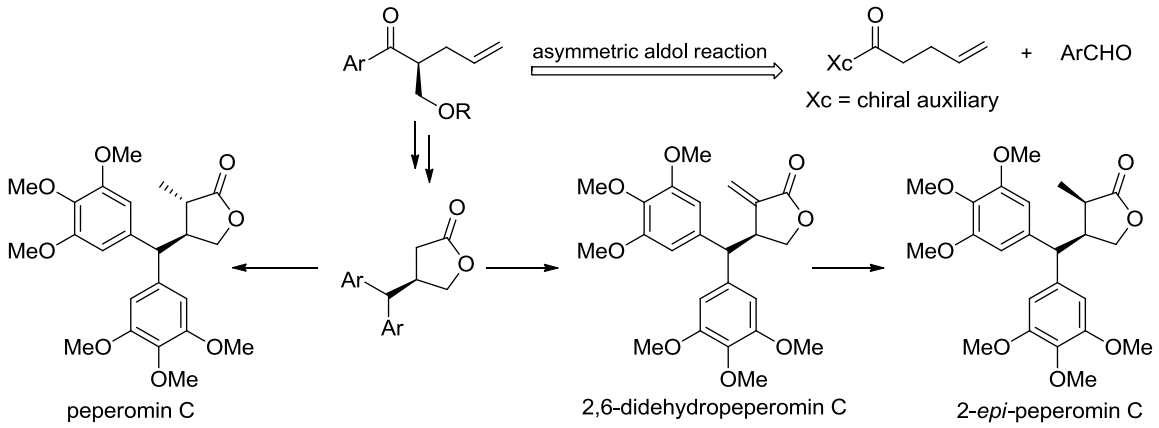
สนับสนุนโดยสำนักงานคณะกรรมการการอุดมศึกษา สำนักงานกองทุนสนับสนุนการวิจัย

และมหาวิทยาลัยมหิดล

สารบัญ

บทคัดย่อ

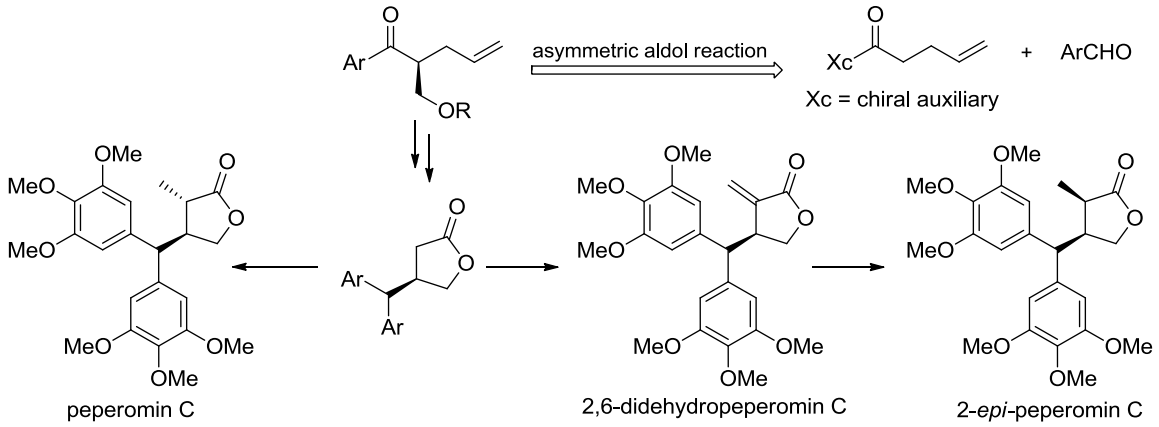
งานวิจัยนี้เป็นการศึกษาและพัฒนาวิธีการสังเคราะห์แบบ stereoselective เพื่อนำไปใช้ในการสังเคราะห์สารธรรมชาติประเภทเซโคลิกแนน โดยที่วิธีการสังเคราะห์ที่พัฒนาในงานวิจัยนี้จะใช้ปฏิกิริยาอัลดอลแบบอสมมาตร (asymmetric aldol reaction) เป็นปฏิกิริยาหลักเพื่อควบคุมการสร้างจุดที่เป็นไครัล (stereogenic center) ที่คาร์บอนในตำแหน่งเบต้าของเซโคลิกแนนเป้าหมาย ในงานวิจัยนี้ ผู้วิจัยได้แสดงให้เห็นถึงความสำคัญของวิธีการสังเคราะห์ที่พัฒนาขึ้น โดยได้นำไปใช้ในการสังเคราะห์สารประเภทเซโคลิกแนนที่สกัดได้จากธรรมชาติ คือเพเพอโรมิน ซี และอนุพันธ์ ได้แก่ 2,6-ไดดีไฮโดรเพเพอโรมินซี และ 2-อิพิเพเพอร์โรมินซี



คำสำคัญ: เซโคลิกแนน; เพเพอโรมินส์; ปฏิกิริยาอัลดอลแบบอสมมาตร

Abstract

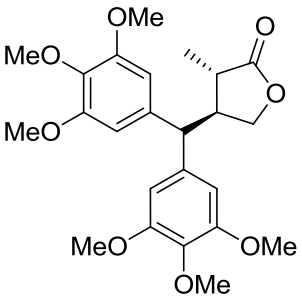
A stereoselective approach to secolignans is described. The key synthetic strategy involves an asymmetric aldol reaction to control the creation of the stereogenic center at the β-carbon of the target secolignans. In the present work, peperomin C and its analogues, i.e., 2,6-didehydropeperomin C and 2-epipeperomin C were successfully synthesized in good yields with high stereoselectivities.



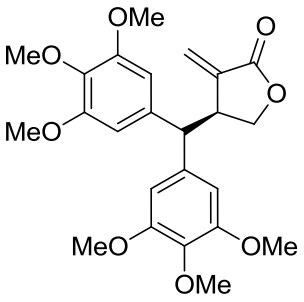
Keywords: Secolignans; Peperomins; Asymmetric aldol reaction

Executive Summary

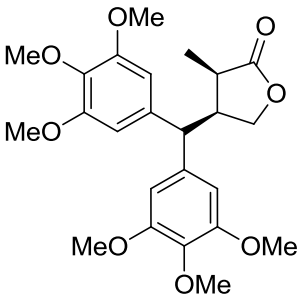
A stereoselective synthetic approach to synthesize peperomin-type secolignans, compounds in subclass of lignans which show a broad range of potent biological acitivities, was developed. Based on this approach, secolignans containing two symmetrical aromatic rings at C-5, such as peperomin C, was obtained in high stereoselectivity. Moreover, its analogues bearing an α-methylene moiety and 2,3-*cis* stereochemistry, i.e., 2,6-didehydropeperomin C and 2-*epi*-peperomin C, respectively, were also readily synthesized in good yields and stereoselectivities. The present approach should found useful for the structure-activity relationship (SAR) study of peperomin-type secolignans since naturally occuring secolignans and their derivatives, varying in the α-substituents and the relative orientation of the α- and β-substituents of γ-butyrolactone ring, could be readily prepared according to our reported methodology.



peperomin C



2,6-didehydropeperomin C



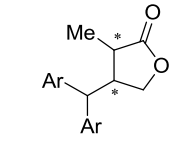
2-*epi*-peperomin C

สัญญาเลขที่ MRG5580046

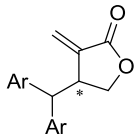
โครงการ: การสังเคราะห์สารประเภทเซโคลิกแนนที่สกัดได้จากพืชสมุนไพรไทยที่มีฤทธิ์ทางชีวภาพ

เนื้อหางานวิจัย

In the present study, the development of an alternative asymmetric synthetic strategy leading to bioactive secolignan natural products (secolignans of type **I** and type **II**) was focused. Our detailed investigations starting from July 2, 2012 to October, 2014 are reported as follow.



Secolignan of type I



Secolignan of type II

1. Retrosynthetic analysis I

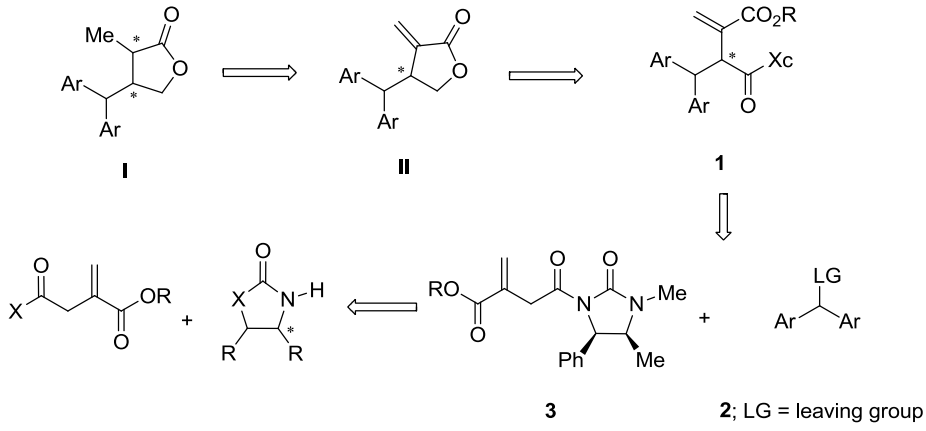
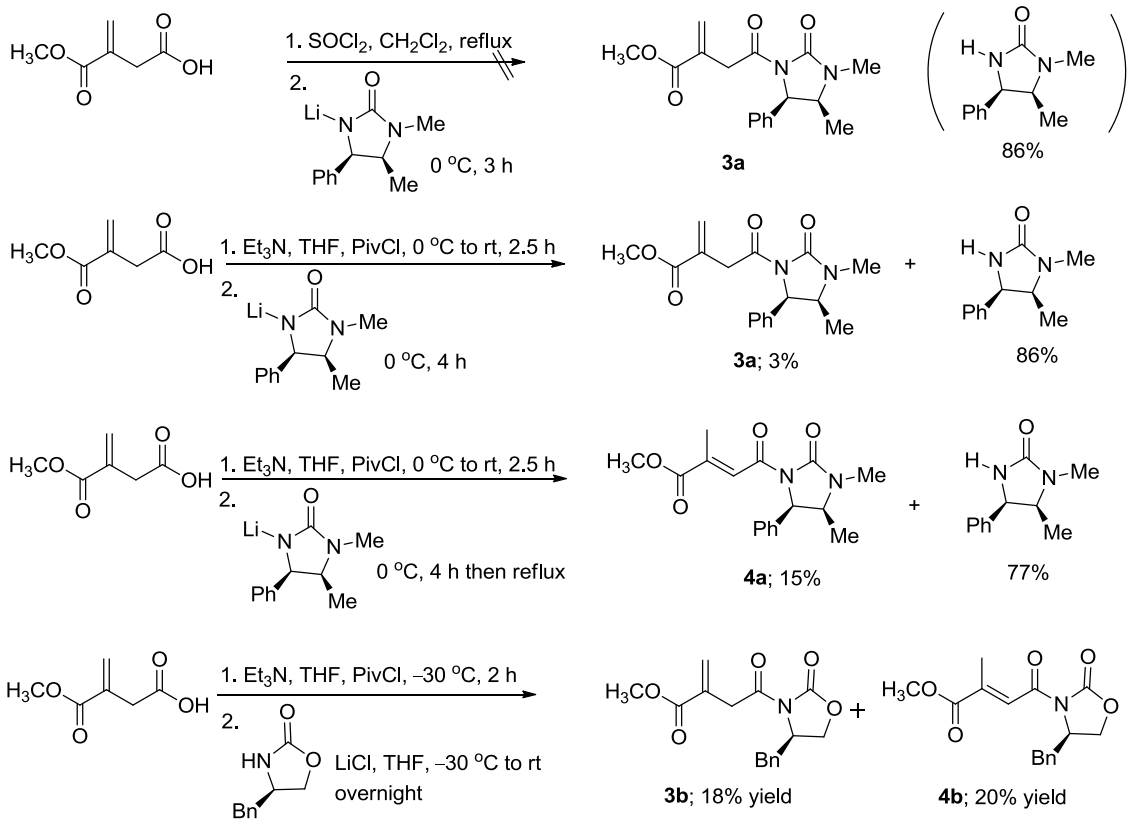


Fig. 1. Retrosynthetic analysis of secolignans of type **I** and type **II**

Initially, asymmetric synthesis of secolignans of type **I** and type **II** was investigated by following the synthetic strategy based on the retrosynthetic analysis depicted in Fig. 1. At first, the preparation of the requisite starting materials of type **3** bearing an α-methylene moiety was focused. We anticipated that compounds **3** would readily be synthesized from the reaction of 3-carboalkoxy-3-butenoic acid derivatives and Evans' chiral auxiliary. However, when 3-carbomethoxy-3-butenoic acid was treated with the chiral auxiliaries, such as (4*R*,5*S*)-(−)-1,5-dimethyl-4-phenyl-2-imidazolidinone and (*R*)-4-benzyl-2-oxazolidinone, under various reported reaction conditions,[1] the reactions gave the expected chiral imides of type **3** in only small quantity as summarized in Scheme 1. The best result was obtained when 3-carbomethoxy-3-butenoic acid was allowed to react with (*R*)-4-benzyl-2-oxazolidinone to give the

expected compound **3b** in only 18% yield together with compound **4b**, obtained *via* the double bond isomerization, in 20% yield. Beside the double bond isomerization, polymerization was also found to be a significant problem in this reaction. Moreover, it should be mentioned here that the separation of compounds **3b** and **4b** by means of chromatography was difficult. These results prompted us to revise our retrosynthetic analysis for the synthesis of secolignans of type **I** and type **II**.



Scheme 1. Attempted preparation of the requisite starting materials of type **3**

2. Retrosynthetic analysis II

We have revised our retrosynthetic analysis for the synthesis of secolignans of type **I** and type **II**. Considering that having an α-methylene moiety in the starting material might be problematic, we therefore decided to install such moiety in the last step of the synthesis. The revised retrosynthetic analysis was as depicted in Fig. 2. We planned to use the reliable and predictable asymmetric aldol addition based on Evans' chiral auxiliary to synthesize the key intermediate **7**. Aldol addition of compound **5** with an aldehyde **6** followed by protection of the hydroxyl group and chemoselective reduction would stereoselectively provide compound **7** which should spontaneously undergo lactonization

to give the corresponding lactone. From the lactone **8**, the key reaction sequences would involve α-methylation and α-methylenation to provide secolignans of type **I** and type **II**, respectively.

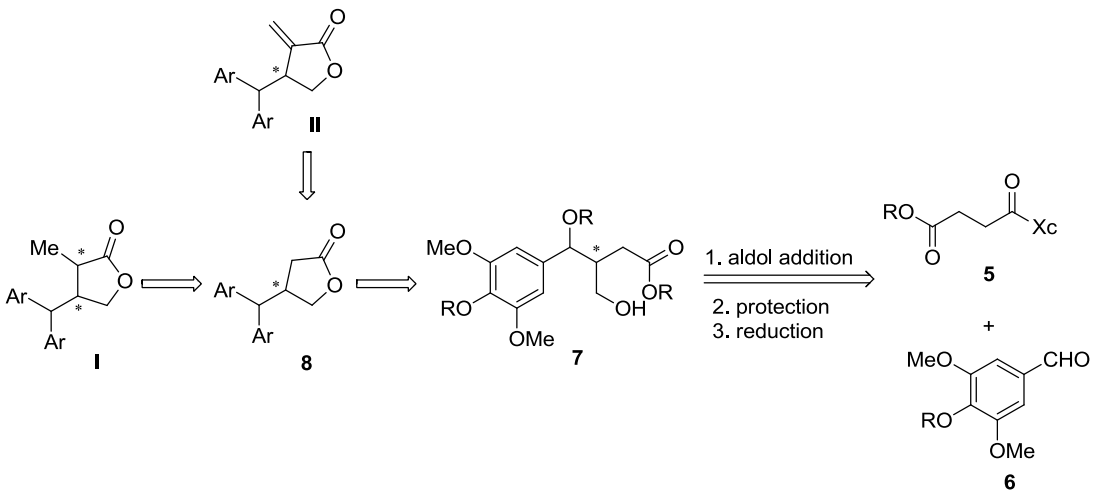
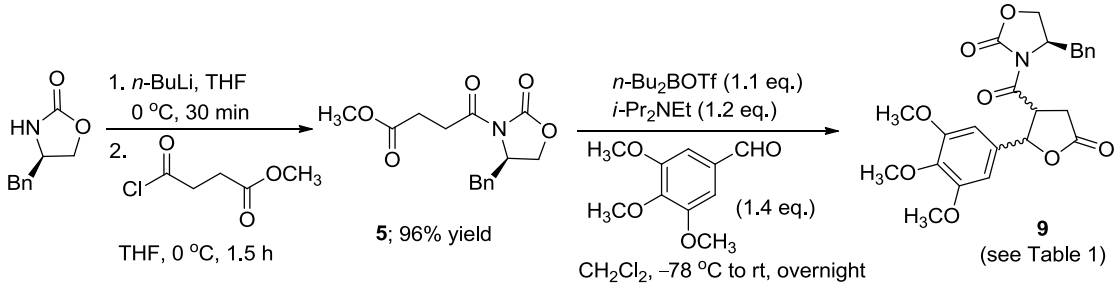


Fig. 2. Retrosynthetic analysis of secolignans of type **I** and type **II**

To begin with, the requisite starting material **5** was readily synthesized and obtained in 96% yield from (*R*)-4-benzyl-2-oxazolidinone and methyl-4-chloro-4-oxobutanoate (Scheme 2). Then, it was subjected to an aldol reaction with 3,4,5-trimethoxybenzaldehyde in the presence of *n*-Bu_2BOTf and *i*-Pr_2NEt in dry CH_2Cl_2.[2] The reaction conditions and the results are summarized in Table 1. Disappointingly, compound **9** was obtained as an inseparable diastereomeric mixtures as determined by ^1H NMR (400 MHz) in all cases. Again, poor diastereoselectivity observed from this reaction prompted us to revise our retrosynthetic analysis.



Scheme 2. Asymmetric aldol addition of **5** with 3,4,5-trimethoxybenzaldehyde

Table 1. Asymmetric aldol addition of **5** with 3,4,5-trimethoxybenzaldehyde

Entry	Reaction conditions	**9**[a]
1	*n*-Bu_2BOTf (2.5 eq.), aldehyde (1.4 eq.), *i*-Pr_2NEt (2.6 eq.) CH_2Cl_2, −78 °C, 20 min	41[b]
2	*n*-Bu_2BOTf (1.2 eq.), aldehyde (1 eq.), *i*-Pr_2NEt (1.5 eq.) CH_2Cl_2, −78 °C to rt, 16 h	35[b]
3	*n*-Bu_2BOTf (1.2 eq.), aldehyde (1 eq.), *i*-Pr_2NEt (1.5 eq.) CH_2Cl_2, −78 °C to rt, 16 h	49[b]
4	*n*-Bu_2BOTf (1.2 eq.), aldehyde (1 eq.), *i*-Pr_2NEt (1.5 eq.) CH_2Cl_2, −78 °C, 4 h	35[b]
5	*n*-Bu_2BOTf (1.1 eq.), aldehyde (1.4 eq.), *i*-Pr_2NEt (1.2 eq.) CH_2Cl_2, −78 °C to rt, 16 h	67[b]

[a] Isolated yield.
[b] Obtained as an inseparable diastereomeric mixture as determined by ^1H NMR (400 MHz).

3. Retrosynthetic analysis III

We planned to use the starting material **10** in place of **5** to perform asymmetric aldol addition with an aldehyde to provide the key intermediate **11** after reductive cleavage of the chiral auxiliary (Fig. 3). From compound **11**, the key reaction sequences will involve arylation, oxidative cleavage of the double bond followed by lactonization to provide lactone **8**. Finally, α-methylation or methylenation should provide compounds **I** or **II**, respectively.

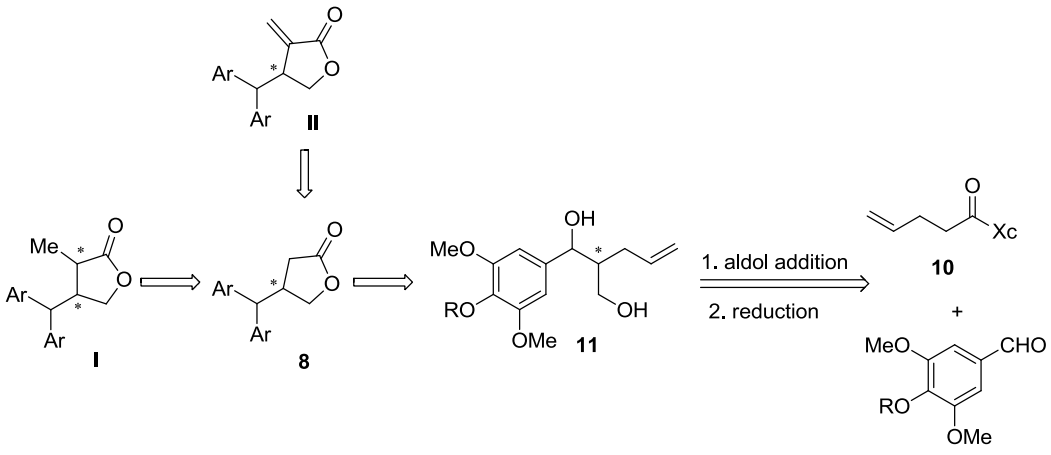
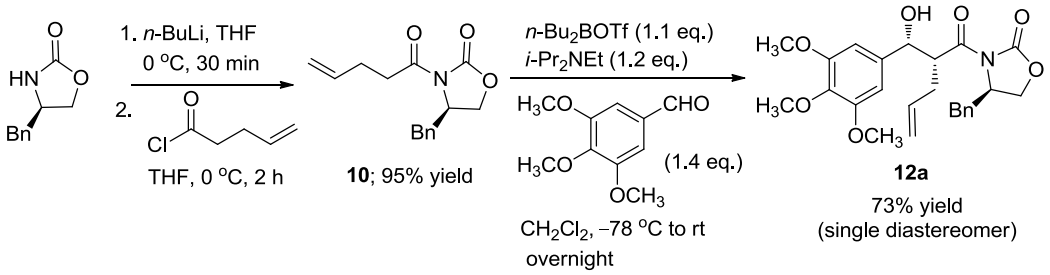


Fig. 3. Retrosynthetic analysis of secolignans of type **I** and type **II**

Chiral imide **10** was synthesized in 95% yield from (*R*)-4-benzyl-2-oxazolidinone and 4-pentenoyl chloride (Scheme 3). Then, it was subjected to an aldol addition with commercially available 3,4,5-trimethoxybenzaldehyde (1.4 eq.) in the presence of *n*-Bu_2BOTf (1.1 eq.) and *i*-Pr_2NEt (1.2 eq.) in dry

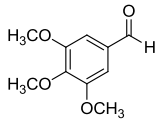
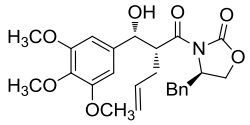
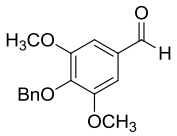
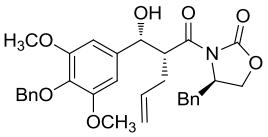
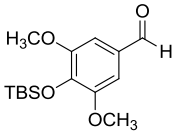
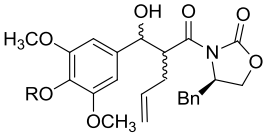
CH_2Cl_2 at −78 °C to rt overnight. To our delight, the *syn*-aldol adduct **12a** was obtained as a single diastereomer in 73% yield and no trace of its diastereomers could be detected by ^{1}H NMR (400 MHz).

The stereochemical outcome of the aldol reaction of compound **10** providing the *syn*-adduct **12a** as a single isomer could be explained on the basis of the well-accepted mechanism involving the Zimmerman–Traxler model as shown in Fig. 4. The aldol additions with other aldehydes were performed and the results are summarized in Table 2. In our cases, it was observed that the reaction was found to be sensitive to the nature of the substituent on an aldehyde partner. Whereas the reaction with 3,4,5-trimethoxybenzaldehyde and 4-(benzyloxy)-3,5-dimethoxy benzaldehyde, prepared from 4-hydroxy-3,5-dimethoxybenzaldehyde, proceeded cleanly to give the corresponding products **12a** and **12b** in moderate to good yields with high stereoselectivity (Table 2, entries 1 and 2), the reaction with 4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethoxybenzaldehyde gave the mixture of products determined by TLC and ^{1}H NMR of the crude mixture (Table 2, entry 3).



Scheme 3. Asymmetric aldol addition of **10** with 3,4,5-trimethoxybenzaldehyde

Table 2. Asymmetric aldol addition of **10** with aldehydes

Entry	Aldehyde	**12**	Isolated yield
1		 **12a**	73 (single diastereomer)
2		 **12b**	56 (single diastereomer)
3		 **12c** (R = TBS or H)	mixture of products

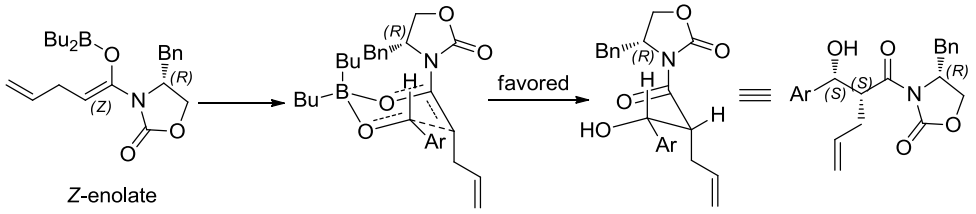
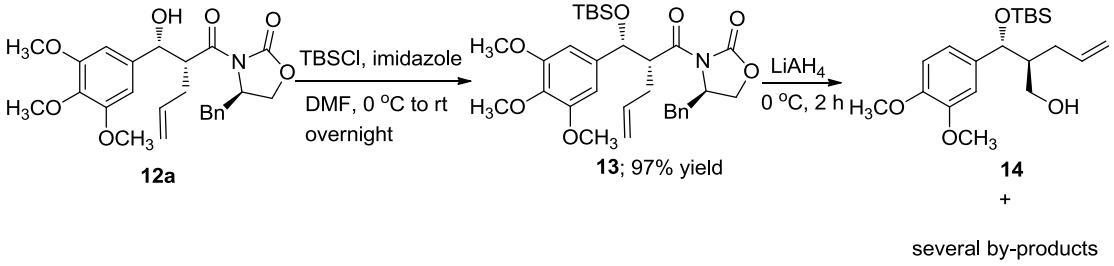


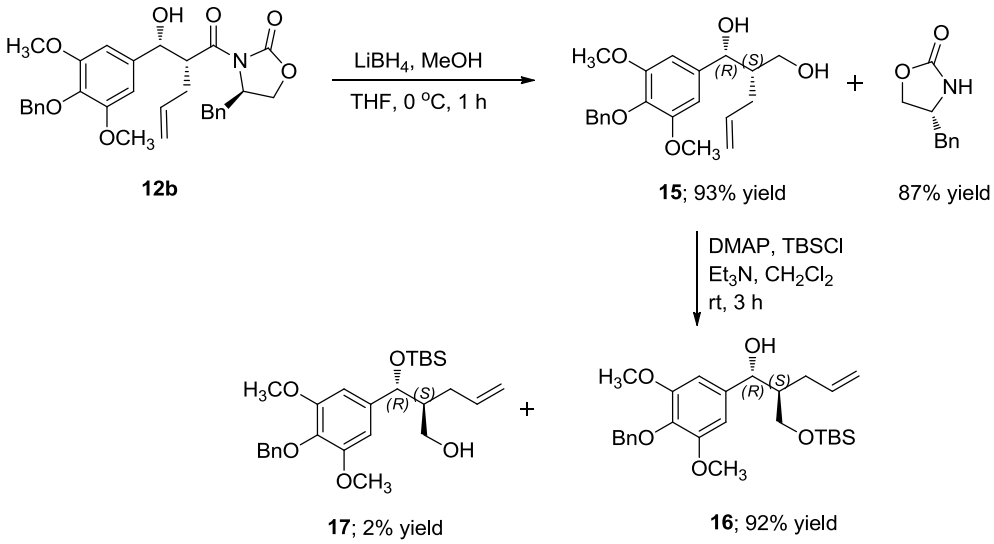
Fig. 4. Proposed transition state for aldol addition of compound **10** with aromatic aldehyds leading to the *syn*-adducts **12a** and **12b**

Aldol adducts **12a** and **12b** can be used as a precursor for asymmetric total synthesis of secolignans **1** and **8**. The protection of the hydroxyl group of *syn*-adduct **12a** as TBS-ether was then carried out (TBSCl, imidazole, DMF) providing the product **13** in 97% yield (Scheme 4). Reductive removal of the chiral auxiliary of **13** was performed by using $LiAlH_4$ expecting to obtain alcohol **14**. Unfortunately, the reaction gave compound **14** together with several by-products as observed by TLC and ^1H NMR of the crude mixture.



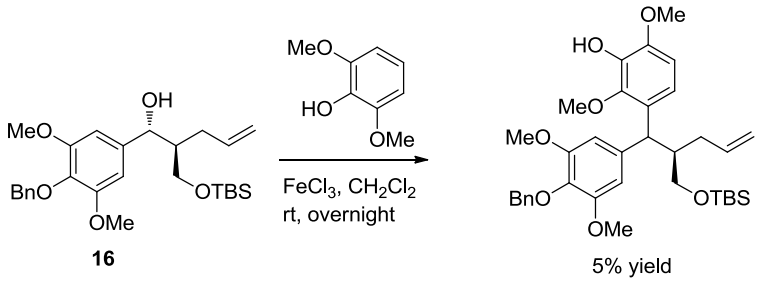
Scheme 4. Protection of **12a** and reductive removal of the chiral auxiliary by using $LiAlH_4$

Meanwhile, the *syn*-adduct **12b** was directly subjected to the reductive cleavage of the chiral auxiliary by using $LiBH_4$ in MeOH and THF[3] at 0 °C for 1 h to cleanly give the diol **15** and the recovered chiral auxiliary in 93 and 87% yields, respectively. Finally, selective protection of the primary hydroxyl group[4] of **15** was carried out to provide mono TBS-protected alcohol **16** and **17** in 92 and 2% yields, respectively (Scheme 5).



Scheme 5. Reductive removal of the chiral auxiliary of **12b** by using $LiBH_4$

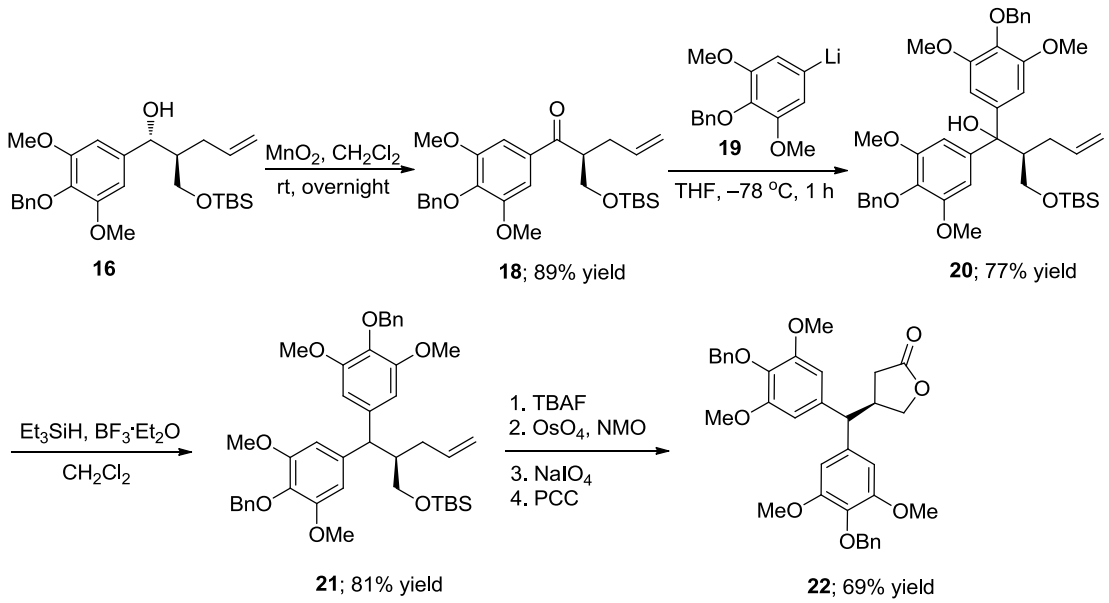
Having chiral compound **16** in hand, we next proceeded with the total synthesis of compounds **1** and **8**. Direct arylation by using $FeCl_3$ mediated Friedel-Craft arylation of 2,6-dimethoxyphenol with **16** led only to the product derived from *ortho*-directed Friedel-Craft arylation (Scheme 6).



Scheme 6. $FeCl_3$ mediated Friedel-Craft arylation

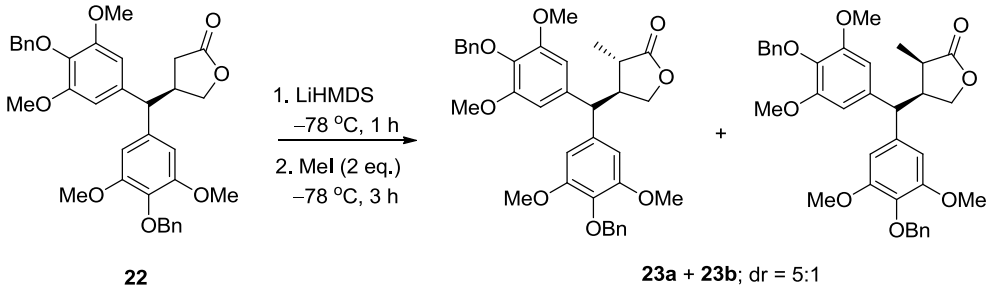
Then, arylation was planned *via* the addition of aryllithium **19** to the ketone **18**, which should be prepared from oxidation of **16**, to give the adduct **20** followed by deoxygenation to provide the product **21** (Scheme 7). Thus, benzylic oxidation of chiral compound **16** by using activated MnO_2 in CH_2Cl_2 at room temperature overnight cleanly gave the expected ketone **18** in 89% yield. Then, ketone **18** was reacted with aryllithium **19** (2 eq.) in THF at −78 °C for 1 h to give the diaryl adduct **20** in 77% yield. Subsequently, compound **20** was subjected to reductive deoxygenation using $Et_3SiH/BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −20 °C to provide the expected product **21** in 81% yield. Desilylation of compound **21** using TBAF gave the corresponding alcohol which was directly subjected to the oxidative cleavage of the double bond (OsO_4, NMO then $NaIO_4$) followed by oxidation of the resulting hemiacetal by using PCC in CH_2Cl_2

to afford the expected lactone **22** in 69% yield after four steps. From the chiral lactone **22**, the synthesis of the naturally occurring secolignans **1** and **8** should be readily accomplished.



Scheme 7. The synthesis of lactone **22**

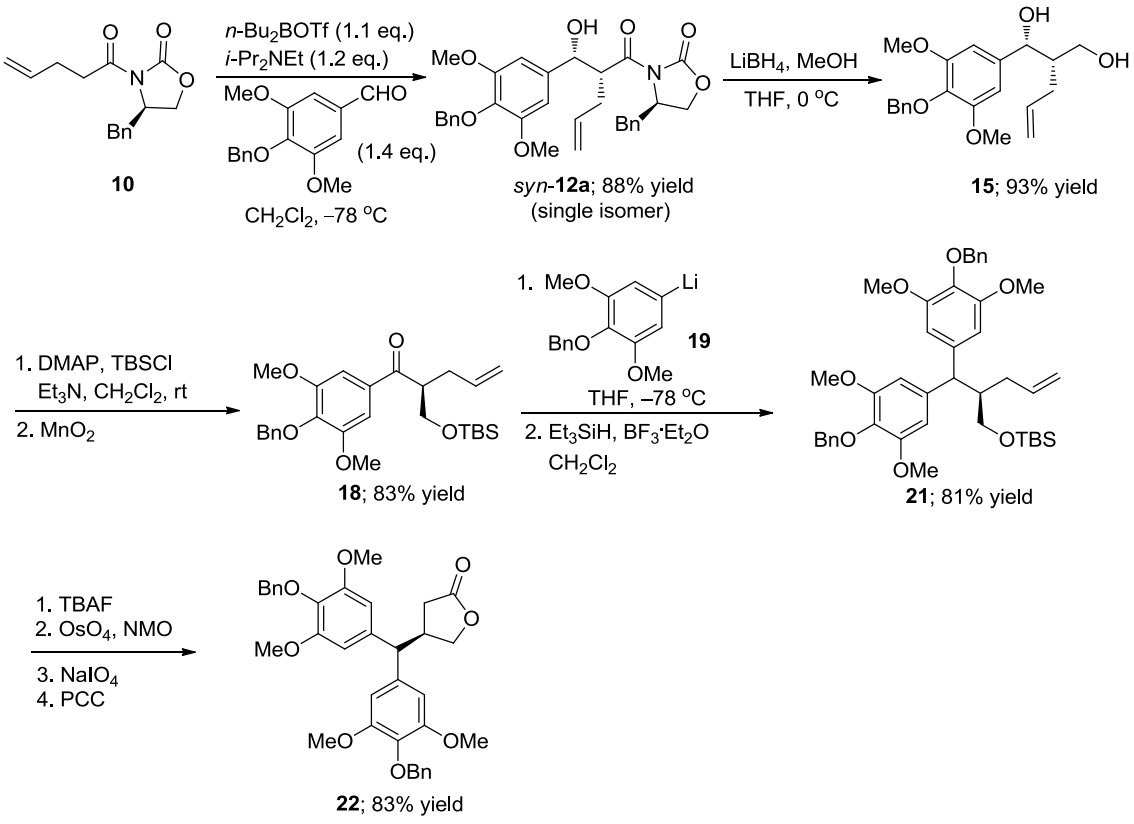
For the synthesis of secolignan **8**, lactone **22** was deprotonated by using LiHMDS (1 eq.) in THF at −78 °C for 1 h and the resulting lithium enolate was allowed to react with methyl iodide (2 eq.) at −78 °C for 3 h to afford the corresponding methylated product **23** as 5:1 diastereomeric ratio determined by ^{1}H NMR (400 MHz) analysis of the crude mixture (Scheme 8).



Scheme 8. Methylation of chiral lactone **22**

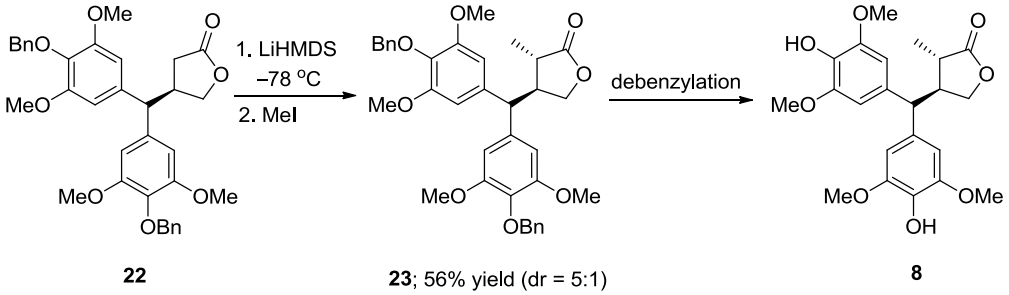
4. Completion of the synthesis

The optimization for the synthesis of the γ-butyrolactone **22** was carried out, and the yield of each steps could be improved as summarized in Scheme 9.



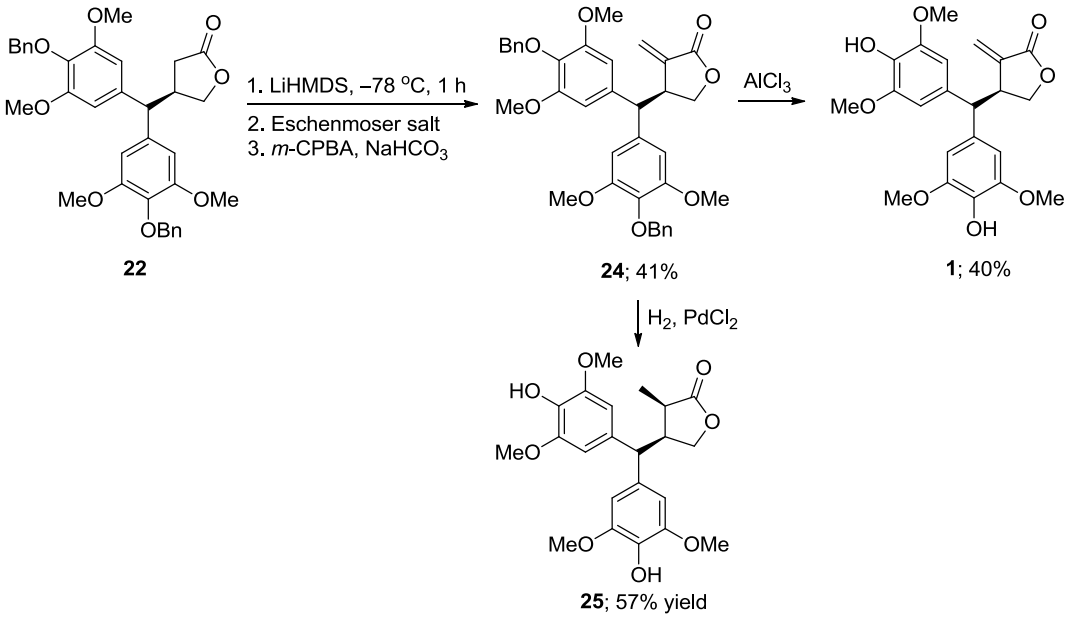
Scheme 9. The synthesis of lactone **22**

The α-methylation of γ-butyrolactone **22** was then carried out as shown in Scheme 10. The reaction provided the corresponding methylated product **23** in 56% yield as a 5:1 mixture of diastereomers as determined by ^{1}H NMR analysis. Attempts to separate the diastereomers of compound **23** by means of chromatography were unsuccessful. From γ-butyrolactone **23**, the synthesis of secolignan **8** can be accomplished after debenzylation.



Scheme 10. The synthesis of secolignan **8**

On the other hand, the synthesis of the target secolignan **1** commenced with treatment of γ-butyrolactone **22** with LiHMDS in THF at −78 °C. The resulting lithium enolated was then allowed to react with Eschenmoser salt followed by treatment with *m*-CPBA under basic conditions to provide α,β-unsaturated γ-butyrolactone **24** in 41% yield. Debenzylation of **24** by using $AlCl_3$ afforded secolignan **1** in 40% yield. Interestingly, we found that hydrogenation of γ-butyrolactone **24** provided compound **25** in 57% yield as a single diastereomer. The stereochemistry of lactone **25** was confirmed by NOE correlation as shown in Fig 5.



Scheme 11. Completion of the synthesis of secolignans **1** and **25**

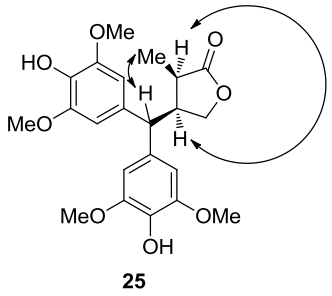
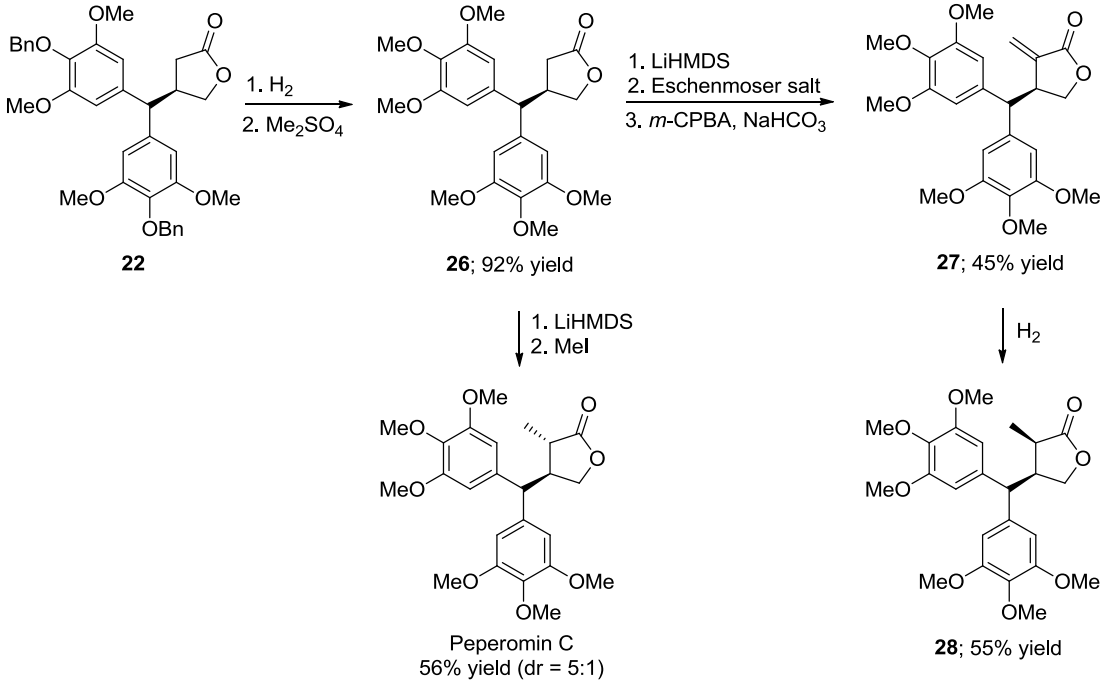


Fig 5. NOE correlation of compound **25**

Furthermore, we have extended our synthetic strategy to synthesize peperomin C and its analogues **27** and **28** as presented in Scheme 12.



Scheme 12. Synthesis of peperomin C and its analogues

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Output ที่ได้จากโครงการ

1. ผลงานวิจัยที่ตีพิมพ์ในวารสารวิชาการระดับนานาชาติ

1.1 ผลงานวิจัยจากโครงการ ที่ได้ตีพิมพ์ไปแล้ว จำนวน 1 เรื่อง

1. Darunee Soorukram,* Jaray Panmuang, Patoomratana Tuchinda, Chutima Kuhakarn, Vichai Reutrakul, Manat Pohmakotr. A stereoselective approach to bioactive secolignans: synthesis of peperomin C and its analogues. *Tetrahedron* **2014**, *70*, 7577-7583.

1.2 ผลงานวิจัยที่มี Acknowledgement โครงการนี้ ที่ได้ตีพิมพ์ไปแล้ว จำนวน 1 เรื่อง

1. Sariya Yodwaree, Darunee Soorukram,* Chutima Kuhakarn, Patoomratana Tuchinda, Vichai Reutrakul, Manat Pohmakotr. Formal synthesis of (+)-3-*epi*-eupomatilone-6 and the 3,5-bis-epimer. *Org. Biomol. Chem.* **2014**, *12*, 6885-6894.

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A stereoselective approach to bioactive secolignans: synthesis of peperomin C and its analogues

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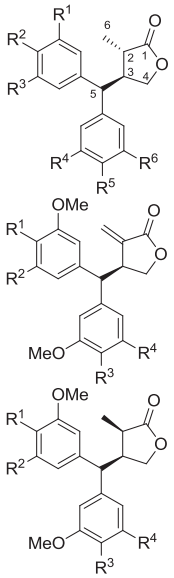
ABSTRACT

A stereoselective approach to secolignans is described. The key synthetic strategy involves an asymmetric aldol reaction to control the creation of the stereogenic center at the β-carbon of the target secolignans. In the present work, peperomin C and its analogues, i.e., 2,6-didehydropeperomin C and 2-*epi*-peperomin C were successfully synthesized in good yields with high stereoselectivities.

1. Introduction

Secolignan is a subclass of lignans[1] found in various plants that have widely been used in Chinese folk medicine. Among those, secolignans, namely peperomins A, B, C, D, and E (Fig. 1) are the well-known representatives.[2] Peperomin-type secolignans show a broad range of potent biological activities. For example, peperomins A–D, the α-methyl-γ-butyrolactone derivatives, have been found to exhibit antitumor,[2d] anti-HIV-1,[2e] and anti-angiogenic[2f] activities. Peperomin E and 2,6-didehydropeperomin B, the α-methylene-γ-butyrolactone derivatives, show inhibitory effects on the growth of cancer cell lines[2c] and anti-inflammatory activity.[2l] In addition, among a variety of peperomins, those containing an α-methylene moiety, such as peperomin E and secolignan **1**, exhibit inhibitory activity against the liver tumor cell.[2d] To date, a variety of bioactive peperomin-type secolignans, varying in the aromatic groups at C-5, the α-substituents (e.g., $-CH_2OH$, $-CH_2OR$, and $-CH_2O$-sugar), and relative orientation of the substituents at the α- and β-positions, have been reported. These include secolignans **2** and **3** bearing a rare 2,3-*cis* configuration.[3]

Due to their broad range of biological activities, peperomin-type secolignans have received considerable attention for further development as potential chemotherapeutic agents.[4] Having taken the importance of structure–activity relationship (SAR) study into account, we therefore aim toward the investigation on the development of a stereoselective methodology that would allow a practical synthesis of naturally occurring secolignans and their derivatives.[5] Herein, we wish to report our synthetic approach



	R^1	R^2	R^3	R^4	R^5	R^6
peperomin A	OMe	-OCH_2O-		OMe	-OCH_2O-	
peperomin B	OMe	OMe	OMe	OMe	-OCH_2O-	
peperomin C	OMe	OMe	OMe	OMe	OMe	OMe
peperomin D	H	-OCH_2O-		H	-OCH_2O-	

	R^1	R^2	R^3	R^4
peperomin E	-OCH_2O-		-OCH_2O-	
2,6-didehydropeperomin B	OMe	OMe	-OCH_2O-	
1	-OCH_2O-		OH	OMe

	R^1	R^2	R^3	R^4
2	-OCH_2O-		-OCH_2O-	
3	OMe	OMe	-OCH_2O-	

Fig. 1. Selected representatives of peperomin-type secolignans.

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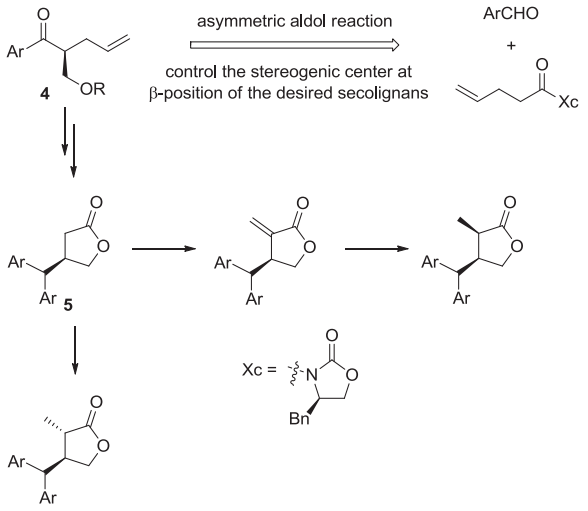
0040-4020/

leading to the stereoselective synthesis of 2,3-*trans*, 2,3-*cis*, and α-methylene peperomin-type secolignans.

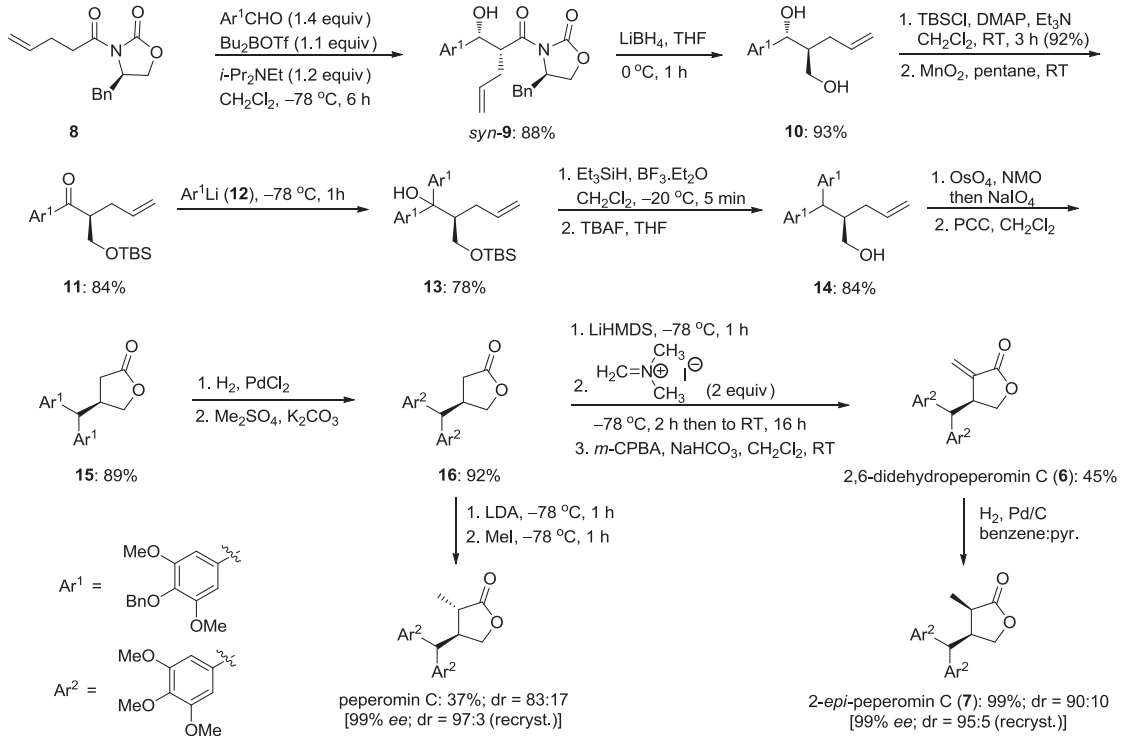
2. Results and discussion

Our synthetic approach is outlined in Scheme 1. We planned to use a chiral oxazolidinone auxiliary (Evans chiral auxiliary)[6] in an asymmetric aldol reaction as a key step to synthesize and control the creation of the stereocenter at an α-carbon of a chiral aryl ketone of type **4**. The chiral intermediate **4** can be converted into 2,3-*trans*, 2,3-*cis* as well as α-methylene secolignans *via* a chiral γ-butyrolactone **5** (Scheme 1). Here we report on stereoselective synthesis of peperomin C and its analogues, 2,6-didehydropeperomin C (**6**) and 2-*epi*-peperomin C (**7**) (Scheme 2).



Scheme 1. Synthetic plan to synthesize chiral aryl ketone **4** as a key synthetic intermediate leading to secolignans.

Our synthesis began with the synthesis of compound **8**.[7] Based on the procedure reported by Evans,[8] compound **8** was treated with 4-(benzyloxy)-3,5-dimethoxybenzaldehyde (Ar^1CHO)[9] in the presence of dibutylboron triflate (Bu_2BOTf) (1.1 equiv) and Hünig's base (*i*-Pr_2NEt) (1.2 equiv) in dry CH_2Cl_2 at −78 °C for 6 h (Scheme 2). Diastereoselective alkylation of the boron enolate derived from compound **8** with aldehyde, Ar^1CHO, proceeded with high diastereoselectivity (>99% dr, 400 MHz ^1H NMR analysis). The desired Evans' *syn* product **9**[10] was obtained in 88% yield as a single diastereomer as determined by ^1H and ^{13}C NMR analyses after chromatographic purification (see Supplementary data). Next, the conversion of the Evans' *syn* product **9** into a chiral ketone **11** was investigated. Thus, reductive cleavage of compound **9** upon treatment with $LiBH_4$[11] in THF at 0 °C for 1 h gave diol **10** (93% yield) and the recovered oxazolidinone auxiliary (87% yield). Selective protection of a primary alcohol moiety of diol **10** was achieved in high yield and selectivity by treatment of the diol **10** with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) and Et_3N in anhydrous CH_2Cl_2 at room temperature for 3 h.[12] The corresponding mono-TBS-protected alcohol was obtained in 92% yield. Subsequent benzylic oxidation using MnO_2 provided the desired chiral ketone **11** in 84% yield. Having successfully been prepared, the chiral ketone **11** was employed as a key substrate for further manipulation directed the synthesis of peperomin C and its analogues **6** and **7**. Thus, treatment of ketone **11** with [4-(benzyloxy)-3,5-dimethoxyphenyl]lithium (**12**) in THF at −78 °C for 1 h gave the corresponding diaryl alcohol **13** (78% yield). Subsequent reductive deoxygenation of the diaryl alcohol **13** was accomplished by treatment of **13** with Et_3SiH and $BF_3{\cdot}Et_2O$ in anhydrous CH_2Cl_2 at −20 °C for 5 min followed by removal of the TBS ether by using TBAF providing the required alcohol **14** (84% yield, two steps). Conversion of the alcohol **14** to chiral γ-butyrolactone **16** was achieved by a two-step reaction involving oxidative cleavage of the terminal alkene moiety of **14** followed by successive oxidation. After examining optimal conditions, it was found that treatment of **14** with OsO_4 (5 mol %), *N*-



Scheme 2. A stereoselective synthesis of peperomin C and its analogues **6** and **7**.

methylmorpholine-*N*-oxide (NMO) (3 equiv) then $NaIO_4$ (2 equiv) followed by oxidation of the resulting lactol by using pyridinium chlorochromate (PCC) in CH_2Cl_2 provided γ-butyrolactone **15** in 89% yield. Debenzylation of **15** followed by methylation of the resulting phenol product afforded γ-butyrolactone **16** in 92% yield. The synthesized γ-butyrolactone **16** shows a specific optical rotation value of $[\alpha]_D^{22}$ −13.5 (*c* 1.0, $CHCl_3$), which is consistent with that reported in the literature {$[\alpha]_D^{25}$ −13.0 (*c* 1.0, $CHCl_3$)}.[13]

For the synthesis of peperomin C, γ-butyrolactone **16** was treated with LDA (1 equiv) in THF at −78 °C followed by trapping with methyl iodide at −78 °C for 1 h. Peperomin C, together with 2-*epi*-peperomin C (**7**), was obtained in 37% yield as an 83:17 mixture of diastereomers as determined by ^1H NMR analysis. Comparable results were obtained when LiHMDS was used as a base in place of LDA. Attempts to separate peperomin C and **7** by means of chromatographic methods were unsuccessful. Fortunately, up to 97:3 diastereomeric ratio of peperomin C (15% yield) with 99% *ee* as determined by HPLC analysis (Daicel Chiral OD-H column; *i*-PrOH/hexane)[14] could be obtained after recrystallization from EtOAc/hexanes. The synthesized peperomin C shows a specific optical rotation value of $[\alpha]_D^{24}$ +27.3 (*c* 0.68, $CHCl_3$) {lit.[2a] $[\alpha]_D^{27}$ +42.7 (*c* 0.06, $CHCl_3$)}. Its ^1H and ^{13}C NMR data are in agreement with those reported for the natural compound (see Supplementary data).

Starting from γ-butyrolactone **16**, a 2,6-didehydropeperomin C (**6**) can be readily synthesized. Eschenmoser methylenation of **16** was carried out according to the previously reported procedure by Danishefsky.[15] Thus, the γ-butyrolactone **16** was treated with LiHMDS (1.5 equiv) in THF at −78 °C for 1 h followed by trapping with the Eschenmoser salt (2 equiv) and the resulting was maintained at −78 °C (2 h) and at room temperature (16 h). Without purification, the corresponding adduct was subsequently treated with *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of $NaHCO_3$. The desired 2,6-didehydropeperomin C (**6**) was obtained in 45% yield after chromatographic purification.

Finally, the conversion of 2,6-didehydropeperomin C (**6**) into 2-*epi*-peperomin C (**7**) should be straightforward through a simple catalytic hydrogenation. It is expected that the bulkiness of the β-diarylmethyl group of **6** would direct the hydrogenation process to take place from the opposite site in order to avoid the steric interaction leading to 2-*epi*-peperomin C (**7**) with a 2,3-*cis* stereochemistry as a major diastereomer. Therefore, catalytic hydrogenation of **6** (H_2, Pd/C, EtOH)[16] provided **7** in 91% yield with good diastereoselectivity (dr=90:10) as determined by ^1H NMR analysis. Similar results were obtained when pyridine was used as a co-solvent for hydrogenation (H_2, Pd/C) in dry benzene;[17] **7** was obtained in 99% yield (dr=90:10). Compound **7** (12% yield; 99% *ee*) with the diastereomeric ratio up to 95:5 as determined by HPLC analysis (Daicel Chiral OD-H column; *i*-PrOH/hexane)[14] could be obtained after recrystallization from EtOAc/hexanes. The 2,3-*cis* stereochemistry of **7** was confirmed from NOE experiments as depicted in Fig. 2 (see Supplementary data). Irradiation of H-3 resulted in an NOE enhancement for H-2. Additionally, upon irradiation of $-CH_3$-6, an NOE enhancement was observed for H-5.

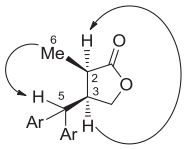


Fig. 2. The key NOE correlations of 2-*epi*-peperomin C (**7**).

3. Conclusions

In conclusion, we have reported a stereoselective approach to synthesize peperomin-type secolignans. Based on this approach, secolignans containing two symmetrical aromatic rings at C-5, such as peperomin C, were obtained in high stereoselectivity. Moreover, its analogues bearing an α-methylene moiety and 2,3-*cis* stereochemistry, i.e., 2,6-didehydropeperomin C and 2-*epi*-peperomin C, respectively, were also readily synthesized in good yields and stereoselectivities. The present approach should be found useful for the SAR study of peperomin-type secolignans since naturally occurring secolignans and their derivatives, varying in the α-substituents and the relative orientation of the α- and β-substituents of γ-butyrolactone ring, could be readily prepared according to our reported methodology.

4. Experimental section

4.1. General

The ^1H NMR spectra were recorded on a Bruker DPX-300 (300 MHz) or a Bruker-400 (400 MHz) spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker DPX-300 (75 MHz) or a Bruker-400 (100 MHz) spectrometer in $CDCl_3$. The chemical shifts are reported as δ-values in parts per million (ppm) relative to the deuterated solvent peak; $CDCl_3$ (δ_H: 7.27, δ_C: 77.0) or TMS (δ_H: 0.00). The IR spectra were recorded on a Perkin Elmer Spectrum GX FT-IR spectrometer. The mass spectra were recorded by using a Thermo Finnigan Polaris Q mass spectrometer. The high-resolution mass spectra were recorded on an HR-TOF-MS Micromass model VQ-TOF2 mass spectrometer. Melting points were recorded on a Buchi M-565 melting Point Apparatus and uncorrected. HPLC was performed with Agilent 1100 Series HPLC Value System using *i*-PrOH/hexanes as mobile phase. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl. Dichloromethane (CH_2Cl_2) and pentane were distilled over calcium hydride and stored over activated molecular sieves (4 Å). Methanol (MeOH) was distilled over Mg powder. Column chromatography was performed by using Merck silica gel 60 (Art 7734). Other common solvents [CH_2Cl_2, hexanes, ethyl acetate (EtOAc), MeOH, and acetone] were distilled before use.

4.2. (*R*)-4-Benzyl-3-(pent-4-enoyl)oxazolidin-2-one (8)

Compound (**8**) was synthesized according to the literature procedure[7] and obtained (492 mg, 95% yield) as a colorless liquid; R_f (20% EtOAc/hexanes) 0.33; $[\alpha]_D^{23}$ −61.7 (*c* 0.8, $CHCl_3$) {lit.[7d] $[\alpha]_D^{23}$ −55 (*c* 0.8, $CHCl_3$)}; IR (neat): ν_{max} 1777, 1702, 1384, 1211, 916 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H, Ar*H*), 5.90 (ddt, *J*=17.1, 10.3, 6.6 Hz, 1H, C*H*), 5.13 (dd, *J*=17.1, 1.4 Hz, 1H, C*H*H), 5.06 (dd, *J*=10.3, 1.1 Hz, 1H, CH*H*), 4.77–4.64 (m, 1H, C*H*), 4.27–4.17 (m, 2H, CH_2O), 3.32 (dd, *J*=13.4, 3.1 Hz, 1H, C*H*H), 3.20–2.96 (m, 2H, CH_2), 2.79 (dd, *J*=13.4, 9.6 Hz, 1H, CH*H*), 2.55–2.42 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5 (CO), 153.4 (CO), 136.6 (CH), 135.2 (C), 129.4 (2×CH), 128.9 (2×CH), 127.3 (CH), 115.7 (CH_2), 66.1 (CH_2), 55.1 (CH), 37.8 (CH_2), 34.7 (CH_2), 28.1 (CH_2); *m*/*z* (EI) 260 [$(M+H)^+$, 25], 259 (M^+, 100), 231 (17), 178 (28), 117 (29), 91 (44), 55 (50); HRMS (ESI-TOF): MNa^+, found 282.1101. $C_{15}H_{17}NO_3Na$ requires 282.1106.

4.3. (*R*)-4-Benzyl-3-{(*R*)-2-{(*R*)-[4-(benzyloxy)-3,5-dimethoxyphenyl](hydroxy)methyl}pent-4-enoyl}oxazolidin-2-one (9)

To a solution of compound **8** (457 mg, 1.76 mmol) in dry CH_2Cl_2 (4.5 mL) cooled at −78 °C was added a solution of Bu_2BOTf (1 M in CH_2Cl_2, 1.94 mL, 1.94 mmol) dropwise over 10 min. The resulting solution was allowed to stir at −78 °C for 30 min, and then *i*-Pr_2NEt (0.36 mL, 2.6 mmol) was slowly added. After stirring at −78 °C for 45 min, a solution of 4-(benzyloxy)-3,5-dimethoxybenzaldehyde

(528 mg, 1.94 mmol) in dry CH_2Cl_2 (1.7 mL) was added dropwise over 10 min, then the resulting reaction mixture was allowed to stir at −78 °C for 6 h and quenched with phosphate buffer (pH 7, 4 mL) at −78 °C. The cooling bath was replaced by an ice-bath then MeOH (6 mL) was added followed by the addition of a solution mixture of MeOH and 30% aqueous H_2O_2 solution [2:1 (v/v), 6 mL]. After stirring at 0 °C for 1 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL), and then the solvents were removed in vacuo. The resulting residue was dissolved in EtOAc and H_2O and extracted with EtOAc (3×30 mL). The combined organic phase was washed with a saturated aqueous $NaHCO_3$ solution, brine, and dried over anhydrous Na_2SO_4. Purification by column chromatography [SiO_2, 20% EtOAc/hexanes] gave *syn*-aldol product **9** (820 mg, 88% yield) as a pale yellow viscous oil; R_f (40% EtOAc/hexanes) 0.31; $[\alpha]_D^{22}$ −69.9 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3528, 1778, 1690, 1594, 1500, 1463, 1385, 1130 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49–7.44 (m, 2H, Ar*H*), 7.34–7.23 (m, 6H, Ar*H*), 7.19–7.14 (m, 2H, Ar*H*), 6.62 (s, 2H, Ar*H*), 5.95–5.80 (m, 1H, C*H*), 5.12 (dd, *J*=17.1, 1.2 Hz, 1H, C*H*H), 5.05 (d, *J*=10.1 Hz, 1H, CH*H*), 4.98 (s, 2H, CH_2O), 4.88 (d, *J*=6.2 Hz, 1H, C*H*), 4.51 (ddd, *J*=10.1, 6.2, 4.1 Hz, 1H, C*H*), 4.39–4.32 (m, 1H, C*H*), 3.99 (dd, *J*=9.0, 2.4 Hz, 1H, C*H*H), 3.82 (s, 6H, 2×OCH_3), 3.79 (dd, *J*=8.5, 8.5 Hz, 1H, CH*H*), 3.19 (dd, *J*=13.4, 3.2 Hz, 1H, C*H*H), 2.73–2.53 (m, 4H, CH*H*, CH_2 and O*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4 (CO), 153.4 (2×C), 153.1 (CO), 137.7 (C), 137.0 (C), 136.2 (C), 135.2 (CH), 135.1 (C), 129.3 (2×CH), 128.9 (2×CH), 128.4 (2×CH), 128.1 (2×CH), 127.8 (CH), 127.4 (CH), 117.3 (CH_2), 103.2 (2×CH), 75.0 (CH), 74.9 (CH_2), 65.9 (CH_2), 56.1 (2×CH_3), 55.6 (CH), 49.3 (CH), 38.0 (CH_2), 32.4 (CH_2); *m*/*z* (EI) 531 (M^+, 13), 336 (23), 263 (27), 181 (23), 91 (100); HRMS (ESI-TOF): MNa^+, found 554.2147. $C_{31}H_{33}NO_7Na$ requires 554.2155.

4.4. (1*R*,2*S*)-2-Allyl-1-[4-(benzyloxy)-3,5-dimethoxyphenyl] propane-1,3-diol (10)

To a solution of *syn*-aldol adduct **9** (539 mg, 1.0 mmol) in dry THF (3 mL) cooled at 0 °C were added dry MeOH (90 μL, 2.2 mmol) and a solution of $LiBH_4$ (51 mg, 2.3 mmol) in dry THF (3.5 mL) under an argon atmosphere. The reaction mixture was stirred at 0 °C for 1 h, then quenched with an aqueous NaOH solution (1 M, 3 mL) and extracted with EtOAc (3×30 mL). The combined organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification by column chromatography [SiO_2, 100% Et_2O] gave the diol **10** (336 mg, 93% yield) as a colorless liquid; R_f (100% Et_2O) 0.25; $[\alpha]_D^{22}$ +15.0 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3407, 1639, 1592, 1504, 1456, 1419, 1328, 1234, 1127, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J*=6.7 Hz, 2H, Ar*H*), 7.29–7.17 (m, 3H, Ar*H*), 6.46 (s, 2H, Ar*H*), 5.66 (ddt, *J*=17.0, 10.0, 7.1 Hz, 1H, C*H*), 5.00–4.89 (m, 2H, C*HH*), 4.92 (s, 2H, CH_2O), 4.81 (d, *J*=4.1 Hz, 1H, C*H*), 3.72 (s, 6H, 2×OCH_3), 3.65–3.52 (m, 2H, CH_2), 2.08–1.95 (m, 2H, CH_2), 1.90–1.81 (m, 1H, C*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2 (2×C), 138.3 (C), 137.7 (C), 137.0 (CH), 135.7 (C), 128.4 (2×CH), 128.0 (2×CH), 127.8 (CH), 116.4 (CH_2), 103.1 (2×CH), 76.1 (CH), 74.9 (CH_2), 63.7 (CH_2), 56.0 (2×CH_3), 46.2 (CH), 29.8 (CH_2); *m*/*z* (EI) 358 (M^+, 36), 341 (20), 273 (19), 267 (29), 249 (34), 156 (100), 124 (17), 91 (40); HRMS (ESI-TOF): MNa^+, found 381.1678. $C_{21}H_{26}O_5Na$ requires 381.1678.

4.5. (*S*)-1-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-2-{[(*tert*-butyldimethylsilyl)oxy]methyl}pent-4-en-1-one (11)

To a mixture of diol **10** (307 mg, 0.85 mmol) and DMAP (10 mg, 0.085 mmol) in dry CH_2Cl_2 (3 mL), Et_3N (0.36 mL, 2.55 mmol) was added. The resulting reaction mixture was then treated with a solution of TBSCl (384 mg, 2.55 mmol) in dry CH_2Cl_2 (3 mL) at room temperature. The progress of the reaction was monitored by TLC. After the complete consumption of the starting material (3 h), the reaction mixture was quenched with H_2O (5 mL) and extracted with EtOAc (3×30 mL). The combined organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification by column chromatography [SiO_2, 20% EtOAc/hexanes] gave the corresponding mono-TBS protected alcohol (370 mg, 92% yield) as a colorless liquid; R_f (20% EtOAc/hexanes) 0.40; $[\alpha]_D^{22}$ +14.4 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3486, 1592, 1504, 1463, 1328, 1252, 1232, 1130, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J*=7.1 Hz, 2H, Ar*H*), 7.27–7.16 (m, 3H, Ar*H*), 6.48 (s, 2H, Ar*H*), 5.66–5.54 (m, 1H, C*H*), 4.97–4.90 (m, 2H, C*HH*), 4.92 (s, 2H, CH_2O), 4.90–4.86 (m, 1H, C*H*), 3.73 (s, 6H, 2×OCH_3), 3.70 (d, *J*=2.6 Hz, 1H, O*H*), 3.67 (d, *J*=4.0 Hz, 2H, CH_2), 2.14–1.94 (m, 2H, CH_2), 1.83–1.75 (m, 1H, C*H*), 0.85 [s, 9H, Si(CH_3)$_3$], 0.01 (s, 3H, SiCH_3), 0.00 (s, 3H, SiCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2 (2×C), 138.6 (C), 137.9 (C), 137.1 (CH), 135.6 (C), 128.5 (2×CH), 128.0 (2×CH), 127.7 (CH), 116.4 (CH_2), 103.1 (2×CH), 76.6 (CH), 74.9 (CH_2), 64.5 (CH_2), 56.1 (2×CH_3), 46.2 (CH), 29.0 (CH_2), 25.8 (3×CH_3), 18.1 (C), −5.5 (CH_3), −5.6 (CH_3); *m*/*z* (EI) 472 (M^+, 46), 367 (100), 323 (24), 231 (30), 211 (94), 91 (51); HRMS (ESI-TOF): MNa^+, found 495.2535. $C_{27}H_{40}O_5SiNa$ requires 495.2543.

To a solution of mono-TBS protected alcohol (1.73 g, 3.66 mmol) in dry *n*-pentane (40 mL) was added MnO_2 (9.56 g, 110 mmol) at room temperature. The resulting brown suspension was stirred at room temperature, and the progress of the reaction was monitored by TLC. After the complete consumption of the starting material (12 h), the reaction mixture was filtered through Celite pad, and the residue was eluted with EtOAc (250 mL). Compound **11** (1.44 g, 84% yield) was obtained as a yellow oil; R_f (20% EtOAc/hexanes) 0.52; $[\alpha]_D^{22}$ +2.3 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 1674, 1584, 1502, 1463, 1415, 1323, 1129, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50–7.45 (m, 2H, Ar*H*), 7.37–7.26 (m, 3H, Ar*H*), 7.22 (s, 2H, Ar*H*), 5.75 (ddt, *J*=17.1, 10.1, 7.0 Hz, 1H, C*H*), 5.15 (s, 2H, CH_2O), 5.05 (dd, *J*=17.1, 1.5 Hz, 1H, C*H*H), 4.99 (d, *J*=10.1 Hz, 1H, CH*H*), 3.92–3.84 (m, 1H, C*H*H), 3.88 (s, 6H, 2×OCH_3), 3.79–3.66 (m, 2H, CH*H* and C*H*), 2.48 (ddd, *J*=14.1, 7.0, 7.0 Hz, 1H, C*H*H), 2.31 (ddd, *J*=14.1, 7.0, 7.0 Hz, 1H, CH*H*), 0.8 [s, 9H, SiC(CH_3)$_3$], 0.0 (s, 3H, SiCH_3), −0.6 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8 (CO), 153.2 (2×C), 141.3 (C), 137.4 (C), 135.4 (CH), 133.4 (C), 128.4 (2×CH), 128.1 (2×CH), 127.9 (CH), 116.8 (CH_2), 106.0 (2×CH), 74.9 (CH_2), 64.9 (CH_2), 56.2 (2×CH_3), 48.6 (CH), 33.4 (CH_2), 25.7 (3×CH_3), 18.1 (C), −5.6 (2×CH_3); *m*/*z* (EI) 471 [(M+H)$^+$, 3], 413 (100), 281 (17), 91 (17). HRMS (ESI-TOF): MNa^+, found 493.2381. $C_{27}H_{38}O_5SiNa$ requires 493.2386.

4.6. (*S*)-1,1-Bis[4-(benzyloxy)-3,5-dimethoxyphenyl]-2-{[(*tert*-butyldimethylsilyl)oxy]methyl}pent-4-en-1-ol (13)

A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with 2-(benzyloxy)-5-bromo-1,3-dimethoxybenzene (142 mg, 0.44 mmol) and dry THF (0.5 mL). The solution was cooled to −78 °C, and then a solution of *n*-BuLi (1.85 M in hexanes, 0.24 mL, 0.44 mmol) was added dropwise, and the stirring was continued for 10 min to provide aryllithium **12**. A solution of compound **11** (106 mg, 0.23 mmol) in dry THF (0.5 mL) was then added dropwise. The resulting yellow solution was allowed to stir at −78 °C for 1 h, then quenched with a saturated aqueous NH_4Cl solution (5 mL) and extracted with EtOAc (3×30 mL). The combined organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography [SiO_2, 20% EtOAc/hexanes] gave **13** (125 mg, 78% yield) as a yellow oil; R_f (20% EtOAc/hexanes) 0.31; $[\alpha]_D^{23}$ −22.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3420, 1591, 1505, 1464, 1416, 1321, 1132, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52–7.45 (m, 4H, Ar*H*), 7.37–7.25 (m, 6H, Ar*H*), 6.81 (s, 2H, Ar*H*), 6.80 (s, 2H, Ar*H*), 5.88–5.77 (m, 1H, C*H*), 5.22 (s, 1H, O*H*), 5.08 (brs, 1H, C*H*H), 5.05 (d, *J*=3.6 Hz, 1H, CH*H*), 5.00 (s, 2H, CH_2O), 4.99 (s, 2H, CH_2O), 3.83 (s, 6H, 2×OCH_3), 3.82 (s, 6H,

2×OCH_3), 3.77 (dd, J=10.0, 2.0 Hz, 1H, CHH), 3.67 (d, J=10.0 Hz, 1H, CHH), 2.56–2.44 (m, 1H, CHH), 2.39 (dd, J=10.0, 1.3 Hz, 1H, CH), 2.24 (dd, J=13.9, 5.7 Hz, 1H, CHH), 0.91 [s, 9H, SiC(CH_3)$_3$], 0.01 (s, 3H, SiCH_3), −0.05 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1 (2×C), 153.0 (2×C), 143.5 (C), 141.7 (C), 137.9 (C), 137.8 (C), 137.2 (CH), 135.5 (C), 135.4 (C), 128.3 (4×CH), 128.0 (4×CH), 127.7 (CH), 127.6 (CH), 116.4 (CH_2), 102.9 (2×CH), 102.8 (2×CH), 81.3 (C), 74.9 (CH_2), 74.8 (CH_2), 62.1 (CH_2), 56.2 (2×CH_3), 56.1 (2×CH_3), 46.1 (CH), 30.0 (CH_2), 25.7 (3×CH_3), 18.0 (C), −5.95 (CH_3), −5.99 (CH_3); m/z (EI) 714 (M^+, 1), 551 (14), 515 (46), 473 (51), 461 (100), 370 (33), 91 (45); HRMS (ESI-TOF): MNa^+, found 737.3482. $C_{42}H_{54}O_8SiNa$ requires 737.3486.

4.7. (*R*)-2-{Bis[4-(benzyloxy)-3,5-dimethoxyphenyl]methyl} pent-4-en-1-ol (14)

To a solution of **13** (788 mg, 1.1 mmol) in dry CH_2Cl_2 (18 mL) cooled at −20 °C under an argon atmosphere was added Et_3SiH (0.88 mL, 5.5 mmol) followed by the addition of $BF_3{\cdot}OEt_2$ (0.4 mL, 3.3 mmol). After the complete consumption of the starting material (5 min), the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography [SiO_2, 20% EtOAc/hexanes] gave the corresponding product (696 mg, 91% yield) as a yellow oil; R_f (20% EtOAc/hexanes) 0.40; $[\alpha]_D^{24}$ −14.1 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 1589, 1506, 1456, 1417, 1326, 1241, 1130, 836 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.49–7.44 (m, 4H, ArH), 7.30–7.24 (m, 6H, ArH), 6.52 (s, 2H, ArH), 6.50 (s, 2H, ArH), 5.78 (ddt, J=17.2, 10.0, 7.1 Hz, 1H, CH), 5.03–4.90 (m, 6H, CHH and 2×CH_2), 3.82 (s, 6H, 2×OCH_3), 3.80 (s, 6H, 2×OCH_3), 3.73 (d, J=10.9 Hz, 1H, CH), 3.53 (dd, J=9.8, 2.8 Hz, 1H, CHH), 3.33 (dd, J=9.8, 4.0 Hz, 1H, CHH), 2.25–2.15 (m, 1H, CH), 2.15–2.02 (m, 2H, CH_2), 0.9 [s, 9H, Si(CH_3)$_3$], −0.05 (s, 3H, SiCH_3), −0.08 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.4 (2×C), 153.3 (2×C), 139.7 (C), 139.5 (C), 137.9 (2×C), 137.0 (CH), 135.6 (C), 135.5 (C), 128.4 (4×CH), 128.1 (4×CH), 127.7 (2×CH), 116.2 (CH_2), 105.6 (2×CH), 105.4 (2×CH), 75.0 (CH_2), 74.9 (CH_2), 61.2 (CH_2), 56.3 (2×CH_3), 56.2 (2×CH_3), 53.3 (CH), 44.5 (CH), 33.0 (CH_2), 25.9 (3×CH_3), 18.3 (C), −5.5 (CH_3), −5.6 (CH_3); m/z (EI) 698 (M^+, 11), 641 (9), 475 (100), 433 (49), 421 (31), 384 (44), 91 (40); HRMS (ESI-TOF): MNa^+, found 721.3537. $C_{42}H_{54}O_7SiNa$ requires 721.3537.

To a solution of the above-mentioned compound (346 mg, 0.5 mmol) in dry THF (1 mL) cooled at 0 °C was added dropwise a solution of TBAF (1 M in THF, 2.6 mL, 2.6 mmol). The reaction mixture was stirred and slowly warmed up to room temperature overnight. The reaction mixture was quenched with H_2O (15 mL) and extracted with EtOAc (3×30 mL). The combined organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography [SiO_2, 40% EtOAc/hexanes] gave **14** (269 mg, 92% yield) as a yellow oil; R_f (40% EtOAc/hexanes) 0.38; $[\alpha]_D^{22}$ −27.2 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3522, 1590, 1506, 1456, 1418, 1326, 1241, 1128, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (brd, J=7.5 Hz, 4H, ArH), 7.36–7.23 (m, 6H, ArH), 6.52 (s, 4H, ArH), 5.90–5.77 (m, 1H, CH), 5.05 (s, 1H, CHH), 5.01 (d, J=8.6 Hz, 1H, CHH), 4.98 (s, 2H, CH_2), 4.96 (s, 2H, CH_2), 3.80 (s, 6H, 2×OCH_3), 3.79 (s, 6H, 2×OCH_3), 3.72 (d, J=11.2 Hz, 1H, CH), 3.61 (dd, J=11.0, 3.6 Hz, 1H, CHH), 3.48 (dd, J=11.0, 4.6 Hz, 1H, CHH), 2.38–2.27 (m, 1H, CH), 2.22–2.12 (m, 1H, CHH), 2.11–2.01 (m, 1H, CHH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5 (2×C), 153.4 (2×C), 139.1 (C), 139.0 (C), 137.8 (2×C), 136.7 (CH), 135.6 (C), 135.5 (C), 128.3 (4×CH), 128.0 (4×CH), 127.7 (2×CH), 116.6 (CH_2), 105.4 (2×CH), 105.1 (2×CH), 74.9 (2×CH_2), 62.6 (CH_2), 56.2 (2×CH_3), 56.1 (2×CH_3), 53.7 (CH), 44.3 (CH), 33.9 (CH_2); m/z (EI) 584 (M^+, 20), 493 (49), 475 (19), 402 (19), 334 (33), 317 (28), 285 (13), 243 (18), 91 (100); HRMS (ESI-TOF): MNa^+, found 607.2668. $C_{36}H_{40}O_7Na$ requires 607.2672.

4.8. (3*R*)-3-{Bis[4′-(benzyloxy)-3′,5′-dimethoxyphenyl] methyl}butyrolactone (15)

To a solution mixture of **14** (190 mg, 0.32 mmol) and NMO (113 mg, 0.96 mmol) in CH_2Cl_2 (13 mL) were added a solution of OsO_4 (2.5% in *t*-BuOH, 0.16 mL, 0.016 mmol) and H_2O (0.16 mL, 8.9 mmol) consecutively at room temperature. The resulting yellow solution was stirred at room temperature, and the progress of the reaction was monitored by TLC. After the complete consumption of the starting material (9 h), $NaIO_4$ (137 mg, 0.64 mmol) was added to the reaction mixture at room temperature. After stirring for 30 min, the reaction mixture was quenched with a saturated aqueous $Na_2S_2O_3$ solution (15 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent, the obtained crude product was dissolved in dry CH_2Cl_2 (13 mL), and PCC (104 mg, 0.48 mmol) was added at room temperature. After stirring for 4 h, the reaction mixture was diluted and extracted with EtOAc (3×30 mL). The combined organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography [SiO_2, 50% EtOAc/hexanes] gave **15** (167 mg, 89% yield) as a pale yellow oil; R_f (50% EtOAc/hexanes) 0.38; $[\alpha]_D^{22}$ −6.4 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max} 1774, 1591, 1505, 1463, 1133 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J=7.1 Hz, 4H, ArH), 7.37–7.24 (m, 6H, ArH), 6.44 (s, 4H, ArH), 4.98 (s, 4H, 2×CH_2), 4.26 (dd, J=9.4, 7.2 Hz, 1H, CHH), 3.99 (dd, J=9.4, 6.8 Hz, 1H, CHH), 3.81 (s, 12H, 4×OCH_3), 3.65 (d, J=11.6 Hz, 1H, CH), 3.36–3.23 (m, 1H, CH), 2.58 (dd, J=17.8, 8.3 Hz, 1H, CHH), 2.29 (dd, J=17.8, 7.7 Hz, 1H, CHH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5 (CO), 153.8 (2×C), 153.7 (2×C), 137.7 (2×C), 137.3 (2×C), 136.2 (C), 136.1 (C), 128.4 (4×CH), 128.1 (4×CH), 127.8 (2×CH), 104.9 (2×CH), 104.8 (2×CH), 74.9 (2×CH_2), 72.0 (CH_2), 56.3 (4×CH_3), 55.6 (CH), 40.3 (CH), 34.1 (CH_2); m/z (EI) 584 (M^+, 23), 493 (100), 461 (31), 403 (17), 371 (29), 334 (26), 317 (77), 181 (20), 91 (98); HRMS (ESI-TOF): MNa^+, found 607.2301. $C_{35}H_{36}O_8Na$ requires 607.2308.

4.9. (3*R*)-3-[Bis(3′,4′,5′-trimethoxyphenyl)methyl]butyrolactone (16)[5b]

Compound **15** (175 mg, 0.3 mmol) and $PdCl_2$ (106 mg, 0.6 mmol) were dissolved in dry MeOH (6 mL) under an argon atmosphere. The argon inlet was replaced by a hydrogen gas balloon, and the reaction mixture was stirred at room temperature. After the complete consumption of the starting material (2 h), the reaction mixture was filtered through Celite pad, and the residue was then washed with EtOAc (150 mL). After removal of the solvent, the obtained crude product was dissolved in acetone (0.25 mL) then $(MeO)_2SO_2$ (0.11 mL, 1.2 mmol) and anhydrous K_2CO_3 (124 mg, 0.9 mmol) were added. The reaction mixture was heated to reflux for 1 h then it was cooled to room temperature and extracted with EtOAc (3×30 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography [SiO_2, 50% EtOAc/hexanes] gave a white solid of **16** in 92% yield (119 mg); R_f (50% EtOAc/hexanes) 0.13; $[\alpha]_D^{22}$ −13.5 (*c* 1.0, $CHCl_3$); mp 168–170 °C (EtOAc/hexanes) [lit.[5b] $[\alpha]_D^{25}$ −13.0 (*c* 1.0, $CHCl_3$); mp 168–169 °C]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.47 (d, J=1.2 Hz, 4H, ArH), 4.30 (dd, J=9.5, 7.2 Hz, 1H, CHH), 4.00 (dd, J=9.5, 6.6 Hz, 1H, CHH), 3.86 (s, 12H, 4×OCH_3), 3.82 (s, 6H, 2×OCH_3), 3.66 (d, J=11.7 Hz, 1H, CH), 3.38–3.28 (m, 1H, CH), 2.61 (dd, J=17.8, 8.3 Hz, 1H, CHH), 2.30 (dd, J=17.8, 7.5 Hz, 1H, CHH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4 (CO), 153.6 (2×C), 153.5 (2×C), 137.6 (2×C), 137.2 (2×C), 104.7 (2×CH), 104.6 (2×CH), 72.0 (CH_2), 60.8 (2×CH_3), 56.2 (4×CH_3), 55.7 (CH),

40.2 (CH), 34.0 (CH_2). ^1H and ^{13}C NMR data of **16** are identical with those reported in the literature.

4.10. Peperomin C

To a solution of *i*-Pr_2NH (50 μL, 0.33 mmol) in dry THF (0.5 mL) cooled at −78 °C under an argon atmosphere was added dropwise *n*-BuLi (1.71 M in hexanes, 0.16 mL, 0.27 mmol). After stirring at −78 °C for 30 min, a solution of **16** (133 mg, 0.3 mmol) in dry THF (0.5 mL) was added dropwise, then the resulting reaction mixture was allowed to stir at −78 °C for 1 h. MeI (20 μL, 0.33 mmol) was then added to the reaction mixture at −78 °C and the stirring was continued for 1 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc (3×30 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography [SiO_2, 50% EtOAc/hexanes] to provide peperomin C as a white solid (50 mg, 37% yield, 83:17 dr). Recrystallization from EtOAc/hexanes gave peperomin C with 99% *ee* and 97:3 dr; R_f (50% EtOAc/hexanes) 0.16; $[\alpha]_D^{24}$ +27.3 (*c* 0.68, $CHCl_3$) {lit.[5b] $[\alpha]_D^{25}$ +43.3 (*c* 0.06, $CHCl_3$), lit.[2a] $[\alpha]_D^{27}$ +42.7 (*c* 0.06, $CHCl_3$)}; mp 149–150 °C (EtOAc/hexanes) [lit.[2a] mp 158–160 °C (MeOH)]; ^1H NMR (400 MHz, $CDCl_3$): δ 6.49 (s, 2H, Ar*H*), 6.48 (s, 2H, Ar*H*), 4.31 (dd, *J*=9.6, 7.6 Hz, 1H, C*H*H), 3.86 (s, 6H, 2×OCH_3), 3.85 (s, 6H, 2×OCH_3), 3.86–3.83 (m, 1H, C*H*H), 3.82 (s, 6H, 2×OCH_3), 3.65 (d, *J*=11.4 Hz, 1H, C*H*), 2.99–2.88 (m, 1H, C*H*), 2.43–2.33 (m, 1H, C*H*), 0.94 (d, *J*=7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.8 (CO), 153.6 (2×C), 153.5 (2×C), 137.5 (2×C), 137.1 (2×C), 104.8 (2×CH), 104.7 (2×CH), 70.4 (CH_2), 60.9 (CH_3), 60.8 (CH_3), 56.6 (CH), 56.3 (4×CH_3), 47.4 (CH), 40.3 (CH), 15.8 (CH_3).

4.11. 2,6-Didehydropeperomin C (6)

To a solution of hexamethyldisilazane (0.1 mL, 0.48 mmol) in dry THF (0.5 mL) cooled at −78 °C under an argon atmosphere was added dropwise *n*-BuLi (1.71 M in hexanes, 0.23 mL, 0.4 mmol). After stirring at −78 °C for 30 min, a solution of **16** (97 mg, 0.22 mmol) in dry THF (0.5 mL) was added dropwise, then the resulting reaction mixture was allowed to stir at −78 °C for 1 h. Eschenmoser's salt (122 mg, 0.66 mmol) was then added to the reaction mixture at −78 °C. After stirring at −78 °C for 30 min, the reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The reaction mixture was diluted with Et_2O (10 mL) then quenched with a saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After removal of solvent, the crude mixture was dissolved in CH_2Cl_2 (3 mL), and a saturated aqueous $NaHCO_3$ solution (1.4 mL) and *m*-CPBA (76 mg, 0.44 mmol) were added. The reaction mixture was stirred at room temperature for 1 h then extracted with CH_2Cl_2 (3×30 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography [SiO_2, 50% EtOAc/hexanes] gave **6** (44 mg, 45% yield) as a white solid; R_f (50% EtOAc/hexanes) 0.28; $[\alpha]_D^{25}$ −7.8 (*c* 0.77, $CHCl_3$); mp 166–167 °C (EtOAc/hexanes); IR ($CHCl_3$): ν_{max} 1761, 1592, 1506, 1464, 1421, 1329, 1242, 1132, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=6.49 (s, 2H, Ar*H*), 6.48 (s, 2H, Ar*H*), 6.16 (d, *J*=2.1 Hz, 1H, CH*H*), 4.87 (d, *J*=2.1 Hz, 1H, CH*H*), 4.34 (dd, *J*=9.6, 7.7 Hz, 1H, CH*H*), 4.03 (dd, *J*=9.6, 4.4 Hz, 1H, C*H*H), 3.86 (s, 6H, 2×OCH_3), 3.85 (s, 6H, 2×OCH_3), 3.83 (s, 6H, 2×OCH_3), 3.90–3.80 (m, 1H, C*H*), 3.74 (d, *J*=11.5 Hz, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.8 (CO), 153.6 (2×C), 153.3 (2×C), 137.3 (C), 137.2 (C), 137.0 (C), 136.8 (C), 135.8 (C), 124.9 (CH_2), 105.3 (2×CH), 104.9 (2×CH), 69.7 (CH_2), 60.9 (CH_3), 60.8 (CH_3), 56.3 (2×CH_3), 56.2 (2×CH_3), 55.8 (CH), 42.7 (CH); *m*/*z* (EI) 444 (M^+, 2), 347 (100), 318 (8); HRMS (ESI-TOF): MNa^+, found 467.1682. $C_{24}H_{28}O_8Na$ requires 467.1682.

4.12. 2-*epi*-Peperomin C (7)

Compound **6** (27 mg, 0.06 mmol) and Pd/C (2 mg) were dissolved in a mixture of dry benzene and pyridine (1:1 v/v, 1 mL) under an argon atmosphere. The argon inlet was replaced by a balloon filled with hydrogen gas, and the reaction mixture was stirred at room temperature. After the complete consumption of the starting material (20 min), the reaction mixture was filtered through Celite pad, and the residue was then washed with MeOH. Compound **7** was obtained as a white solid in 99% yield (26.5 mg, 90:10 dr). Recrystallization from EtOAc/hexanes gave compound **7** with 99% *ee* and 95:5 dr; R_f (40% EtOAc/hexanes) 0.16; $[\alpha]_D^{26}$ −67.7 (*c* 0.46, $CHCl_3$); mp 170–171 °C (EtOAc/hexanes); IR ($CHCl_3$): ν_{max} 1767, 1591, 1506, 1463, 1421, 1329, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.52 (s, 2H, Ar*H*), 6.43 (s, 2H, Ar*H*), 4.06–4.00 (m, 1H, C*H*H), 4.00–3.93 (m, 1H, CH*H*), 3.86 (s, 6H, 2×OCH_3), 3.84 (s, 6H, 2×OCH_3), 3.83 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.74 (d, *J*=12.0 Hz, 1H, C*H*), 3.47–3.34 (m, 1H, C*H*), 2.73 (dq, *J*=7.7, 7.6 Hz, 1H, C*H*), 1.14 (d, *J*=7.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.0 (CO), 153.6 (2×C), 153.2 (2×C), 137.4 (2×C), 137.1 (2×C), 104.4 (2×CH), 104.2 (2×CH), 70.5 (CH_2), 60.9 (CH_3), 60.8 (CH_3), 56.3 (2×CH_3), 56.2 (2×CH_3), 50.8 (CH), 43.2 (CH), 37.5 (CH), 10.5 (CH_3); *m*/*z* (EI) 446 (M^+, 1), 346 (100); HRMS (ESI-TOF): MNa^+, found 469.1833. $C_{24}H_{30}O_8Na$ requires 469.1838.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.07.101.

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Formal synthesis of (+)-3-*epi*-eupomatilone-6 and the 3,5-bis-epimer†

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The formal synthesis of (+)-3-*epi*-eupomatilone-6 (**1**) and the 3,5-bis-epimer (**2**) has been accomplished. The key synthetic strategy involved the stereoselective construction of (3*R*,4*S*,5*R*)- and (3*R*,4*S*,5*S*)-trisubstituted γ-butyrolactones **3** and **4** from (2*R*,3*R*)-2,3-dimethyl-4-pentenoic acid derivative **7**, which was readily obtained *via* stereoselective conjugate addition of vinylmagnesium chloride to a chiral α,β-unsaturated *N*-acyl oxazolidinone (Evans' auxiliary) followed by α-methylation.

Introduction

Lignans, a class of secondary plant metabolites, have been found in a wide variety of plants and were reported to possess a broad range of important biological activities, including antioxidant, anti-inflammatory, antitumor, antifungal, and antiviral activities.[1] Biosynthetically, lignans are formed by the dimerization of two phenylpropanoid units (C6–C3) with a variety of structural differences. Eupomatilones-1–7 (Fig. 1), belonging to a structurally novel subclass of lignans, were first isolated from the Australian shrub *Eupomatia bennettii* in 1991 by Carroll and Taylor.[2] Among the lignan family, the eupomatilones are structurally unusual in that they possess a substituted γ-butyrolactone connected to one of the aromatic rings of the highly oxygenated biaryl skeleton. These unique structural features of eupomatilones have attracted the attention of the organic synthetic community.[3] Despite numerous literature reports, it is still of interest to develop a new asymmetric strategy towards the synthesis of this structurally novel subclass of lignans.

Our interest in the synthesis of eupomatilones and their epimers stems from the relative orientation of three substituents on the lactone core, particularly the adjacent *syn*-dimethyl relationship. Several asymmetric approaches, including asymmetric Sharpless dihydroxylation,[3c] diastereoselective reduction,[3e] and enantioselective desymmetrization of cyclic *meso*-anhydrides,[3i] have been employed as efficient strategies

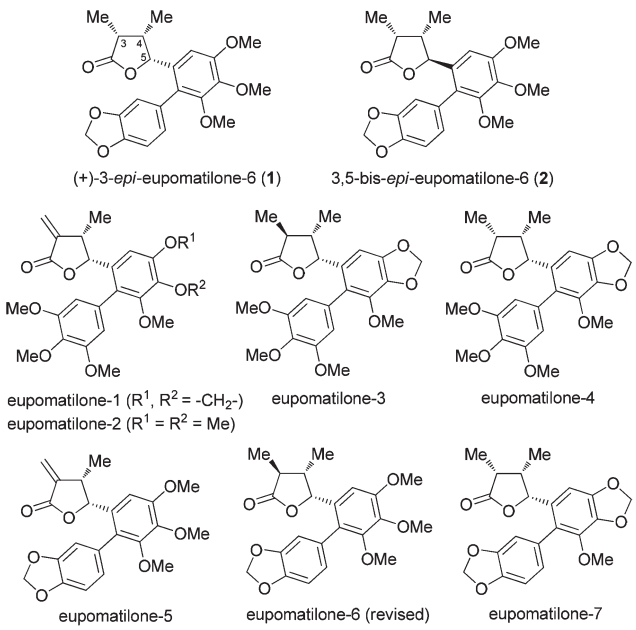

Fig. 1 Structures of eupomatilones.

to install such a relative stereochemistry for the synthesis of 3-*epi*-eupomatilone-6 (**1**) as well as eupomatilone-4 and -7. While several asymmetric approaches to **1** have been reported, there have been few reports on the diastereoselective synthesis of **2**. We report herein the asymmetric strategy towards the synthesis of **1** and the 3,5-bis-epimer (**2**) *via* a stereoselective construction of trisubstituted γ-butyrolactone cores bearing the *syn*-dimethyl stereocenters.

The synthetic plan is outlined in Scheme 1. The oxygenated biaryl motifs of **1** and **2** could be obtained by a halogenation/Suzuki cross-coupling sequence of the key (3*R*,4*S*,5*R*)- and (3*R*,4*S*,5*S*)-γ-butyrolactones **3** and **4**, which in turn should be

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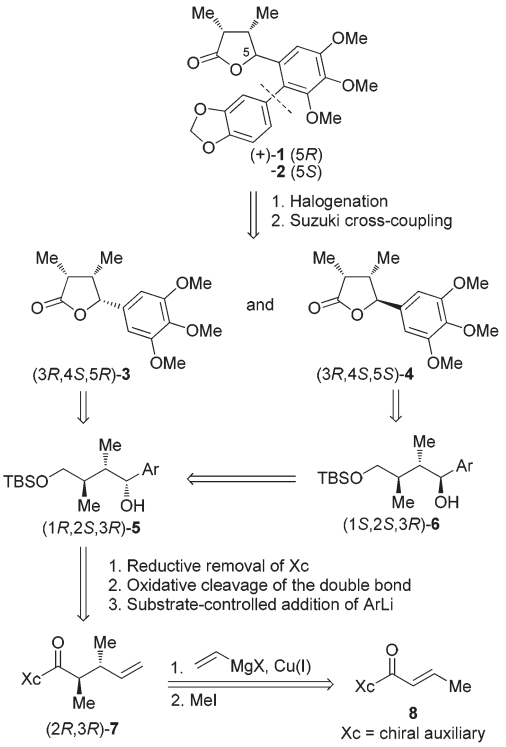
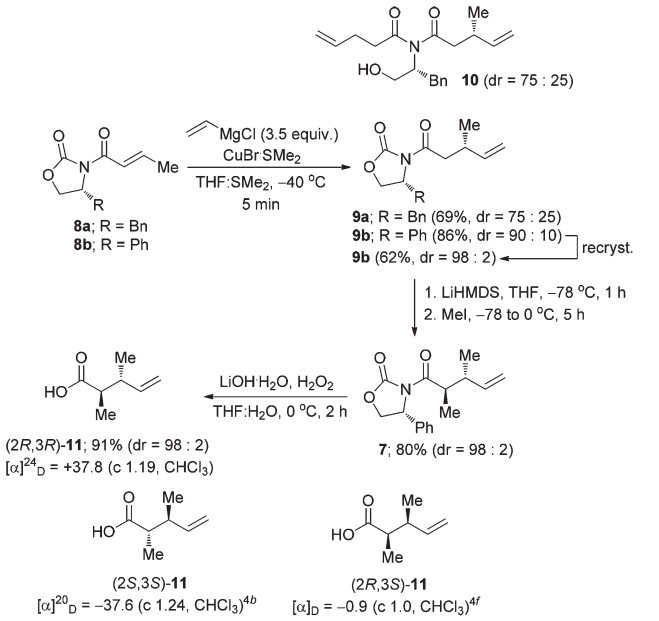
† Electronic supplementary information (ESI) available: Spectroscopic data of all compounds (copies of ^{1}H and ^{13}C NMR), and NOE of compounds **3**, **4**, **16**, **18**, and **19**. See DOI: 10.1039/c4ob01078g



Scheme 1 Synthetic plan for the synthesis of (+)-3-*epi*-eupomatilone-6 (**1**) and the 3,5-bis-epimer (**2**).

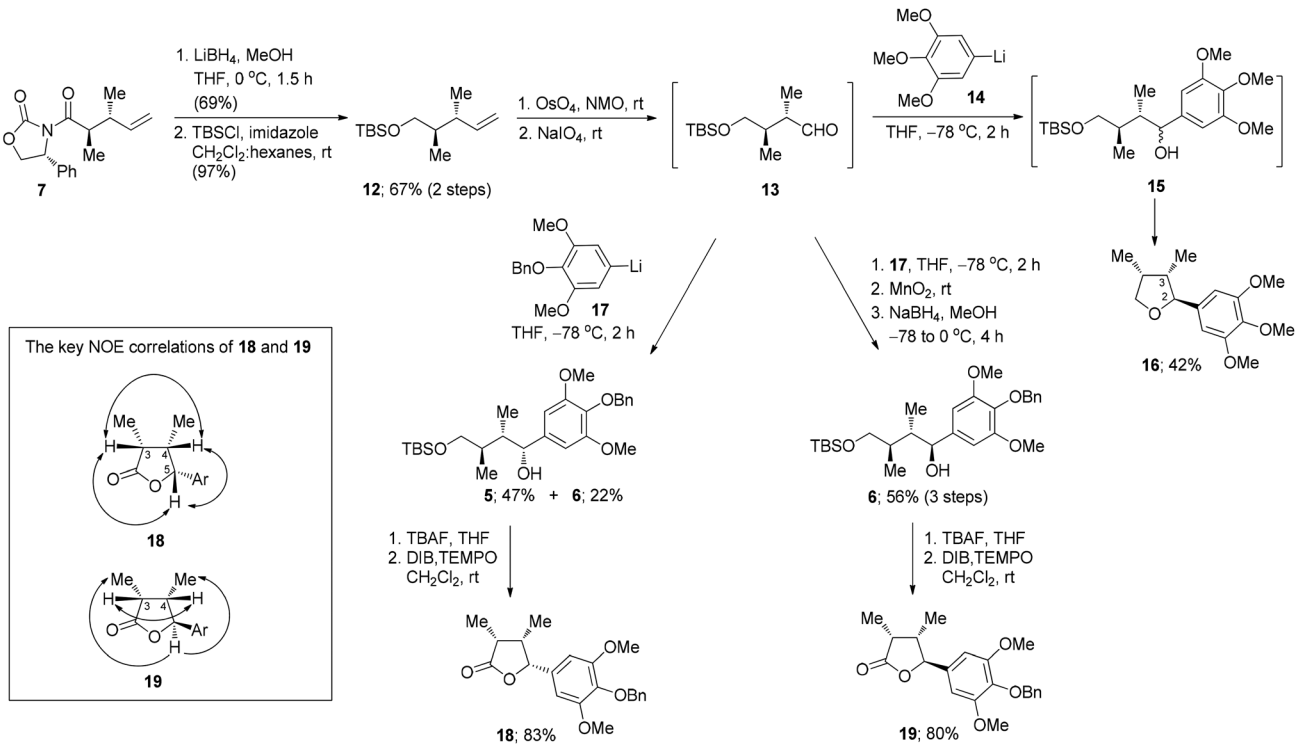


Scheme 2 Asymmetric synthesis of (2*R*,3*R*)-**7**.

readily prepared from (1*R*,2*S*,3*R*)-**5** and (1*S*,2*S*,3*R*)-**6**, respectively, *via* oxidative lactonization reaction. Compounds **5** and **6** could be synthesized stereoselectively from the substrate-controlled addition of aryllithium (ArLi) to an aldehyde derived from (2*R*,3*R*)-2,3-dimethyl-4-pentenoic acid derivatives **7**.[4] Finally, it was envisioned that the (2*R*,3*R*)-**7** could be synthesized by a copper-mediated conjugate addition of vinylmagnesium halides to chiral α,β-unsaturated *N*-acyl oxazolidinones **8** (Evans' chiral auxiliary)[5] followed by α-methylation. Notably, even though the stereoselective conjugate additions of Grignard reagents to *N*-enoyl oxazolidinones[6] and α-enolate alkylations[7] have been studied, less attention has been paid to the stereoselective conjugate addition of vinylmagnesium halides to **8** followed by α-methylation to construct *anti*-2,3-dimethyl-4-pentenoic acid derivatives found in (2*R*,3*R*)-**7**.[8]

Results and discussion

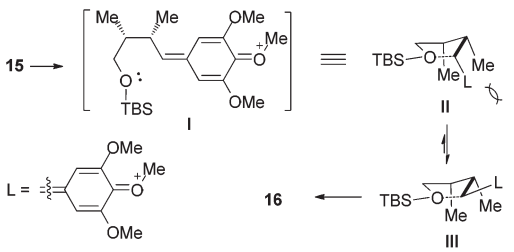
At the outset, asymmetric conjugate addition of vinylmagnesium chloride to compounds **8**[9] was carried out. Initially, the reactions of **8a** with vinylmagnesium chloride under various reaction conditions were screened.[6q–y] In contrast to the reactions using alkyl and arylmagnesium halides,[6a–p] which usually give the corresponding products in good yields with high diastereoselectivity, asymmetric conjugate addition of vinylmagnesium halides often gave lower yields and diastereoselectivity.[6q,y] After a thorough screening, it was found that the reaction of **8a** with commercially available vinylmagnesium chloride (3.5 equiv.) in the presence of CuBr·SMe_2 in THF–SMe_2 (4 : 1) at −40 °C for 1 h gave the desired product **9a** (21%) along with a by-product **10** (19%) (Scheme 2). The structure of compound **10** was confirmed based on its spectroscopic data (see ESI†). Compound **10** was presumably derived from a subsequent reaction of product **9a** with an excess quantity of vinylmagnesium chloride through the addition of vinyl nucleophile to the carbonyl carbon of the oxazolidinone ring of **9a** leading to the ring-opened adduct, which subsequently underwent the second conjugate addition with vinylmagnesium chloride. Significant improvement in the yield of **9a** was obtained by shortening the reaction time (Hughes' procedure).[6w] Thus, the reaction of **8a** with vinylmagnesium chloride at −40 °C for 5 min provided **9a** (69% yield, dr = 75 : 25, 500 MHz ^{1}H NMR analysis) without the detection of **10**. Under similar reaction conditions to those for **8a**, compound **8b** yielded **9b** in good yield with high diastereoselectivity (86% yield, dr = 90 : 10). The diastereomeric ratio (dr) of **9b** was enhanced to 98 : 2 (500 MHz ^{1}H NMR analysis) after a single recrystallization from CH_2Cl_2–hexanes (1 : 9, v/v). Having obtained a precursor **9b** with good yield and high stereoselectivity, we next studied the α-methylation reaction. Thus, compound **9b** (dr = 98 : 2) was treated with LiHMDS in THF at −78 °C followed by methylation using methyl iodide at −78 to 0 °C for 5 h. Gratifyingly, the methylation reaction proceeded stereoselectively to give the desired *anti*-dimethylated product **7** in 80% yield (dr = 98 : 2, 400 MHz ^{1}H NMR analysis). The absolute configuration of **7** was later confirmed after removal of the chiral auxiliary upon hydrolysis to yield chiral 2,3-dimethyl-4-pentenoic acid **11**. Our synthesized compound **11** (dr = 98 : 2, 400 MHz ^{1}H NMR analysis) showed a specific optical rotation value of $[\alpha]_D^{24}$ +37.8 (*c* 1.19, $CHCl_3$) while the known (2*S*,3*S*)-**11**[4b] and (2*R*,3*S*)-**11**[4f] show the values of $[\alpha]_D^{20}$ −37.6 (*c* 1.24, $CHCl_3$) and



Scheme 3 Synthesis of (3*R*,4*S*,5*R*)-**18** and (3*R*,4*S*,5*S*)-**19**.

$[\alpha]_D$ −0.9 (*c* 1.0, $CHCl_3$), respectively. Thus, our synthesized compound **11** was confirmed to be (2*R*,3*R*)-2,3-dimethyl-4-pentenoic acid [(2*R*,3*R*)-**11**)], and compound 7 was confirmed to possess (2*R*,3*R*) configurations. At this stage, it is worth noting that, among the preceding methods that allowed for stereoselective construction of the 2,3-dimethyl stereocenters, our reported procedure serves as a practical approach to create the *anti*-2,3-dimethyl stereocenters found in 2,3-dimethyl-4-pentenoic acid derivatives, such as (2*R*,3*R*)-7.

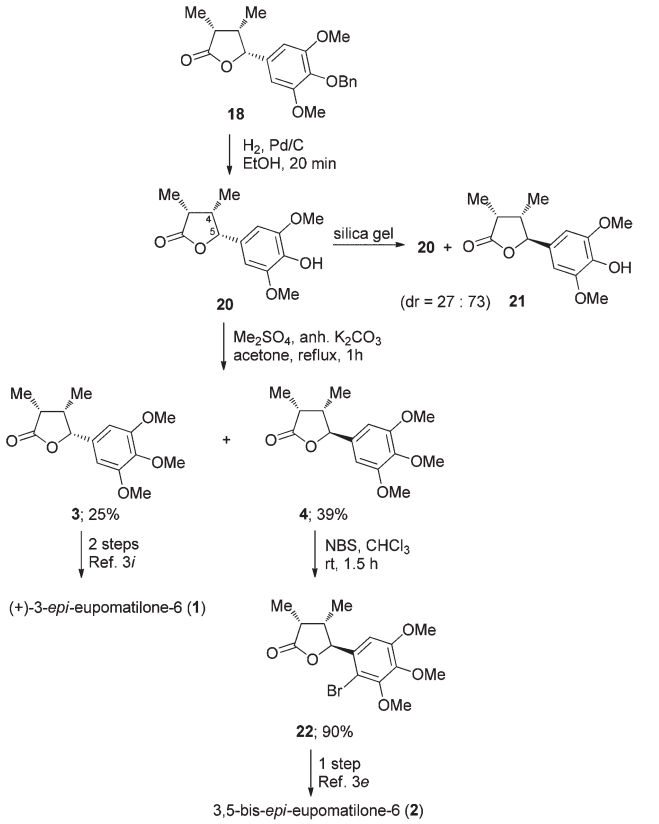
After obtaining the required (2*R*,3*R*)-7 with high stereoselectivity, we next focused our attention on its conversion to compounds **5** and **6** (Scheme 3). Thus, compound 7 (dr = 98 : 2) was subjected to a reductive cleavage of the chiral auxiliary by using $LiBH_4$ in THF with a catalytic amount of methanol[10] at 0 °C for 1.5 h to provide the corresponding alcohol[11] and the recovered chiral auxiliary in 69% and 72% yields, respectively.[12] Subsequently, protection of the initially formed alcohol as a TBS-ether gave compound **12**[13] in 97% yield. Next, oxidative cleavage of the double bond of **12** by using OsO_4 (5 mol%), *N*-methylmorpholine-*N*-oxide (NMO) (3 equiv.) and then $NaIO_4$ (2 equiv.) provided the corresponding aldehyde **13**, which proved to be unstable. Thus, the aldehyde intermediate **13** was further reacted with (3,4,5-trimethoxyphenyl)lithium (**14**; 1.5 equiv.) in THF at −78 °C for 2 h to provide the expected alcohol adduct **15** as a mixture of diastereomers as revealed by ^1H NMR analysis. It was found that the adduct **15** rapidly underwent an intramolecular cyclization to give a trisubstituted tetrahydrofuran **16** in 42% yield (from **12**) as a single diastereomer. The chemical structure of **16** and its stereochemistry were established based on NMR analyses, mass spectrometry, and NOE experiments (see ESI†). The mechanism for the formation of **16** was proposed to proceed *via* the formation of an intermediate oxonium ion **I** followed by an intramolecular cyclization (Scheme 4). The observed stereochemical outcome of **16** (2,3-*anti*-3,4-*syn*) can be explained by the energetically favorable transition state **III** possessing minimized steric interaction between the aryl ring and the adjacent methyl group. To our delight, under similar reaction conditions to those for **14**, the substrate-controlled addition of [4-(benzyloxy)-3,5-dimethoxyphenyl]lithium (**17**; 1.5 equiv.) to aldehyde **13** gave diastereomerically pure adduct **5** (47% yield, major isomer) along with its diastereomer **6** (22% yield, minor isomer); they could be easily separated by simple column chromatography. Alternatively, diastereomeri-



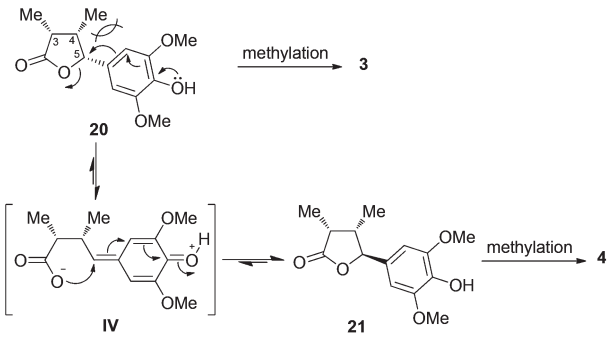
Scheme 4 Proposed reaction mechanism for the formation of **16**.

cally pure compound **6** could be efficiently prepared by the oxidation of a mixture of **5** and **6** to the corresponding ketone followed by stereoselective hydride reduction. In a synthetic sequence, a mixture of **5** and **6** (obtained in 69% yield from the reaction of aldehyde **13** with aryllithium **17**) was treated with MnO_2 at room temperature for 13 h yielding the corresponding ketone (89% yield), which was subsequently subjected to reduction using $NaBH_4$ in MeOH at −78 to 0 °C for 4 h to give the desired compound **6** as a single diastereomer in 89% yield (56% yield, 3 steps). The stereochemical outcome of the addition reaction of **17** to **13** providing **5** as a major diastereomer as well as the hydride reduction of the respective ketone to give **6** as a single diastereomer could be explained on the basis of the Felkin–Ahn model.[14] The stereochemistries of **5** and **6** were also confirmed by the NOE experiments of their corresponding γ-butyrolactone derivatives **18** and **19**, respectively. Desilylation of **5** followed by oxidative lactonization of the corresponding diol using (diacetoxyiodo)benzene (DIB) and 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO)[15] in CH_2Cl_2 at room temperature provided **18** in 83% yield as a single diastereomer. Upon a similar treatment, compound **6** was converted to **19** in 80% yield albeit contaminated with its C-3 epimer (dr = 95 : 5). The NOE experiments confirmed that compound **18** possessed the all-*syn* stereochemistries while compound **19** possessed the 3,4-*syn*-4,5-*anti* stereochemistries (Scheme 3) (see ESI†). Furthermore, the 4,5-*syn* stereochemistry of **18** was further confirmed by the chemical shift of the methyl group at C-4. The influence exerted by an anisotropic effect of the aromatic ring at C-5 (Ar-5) made the methyl group at C-4 of **18** appear at a higher field region (δ = 0.49 ppm) while that of **19** appeared at δ = 1.04 ppm.

Having accomplished the stereoselective synthesis of γ-butyrolactones **18** and **19** containing all requisite absolute stereochemistries, we then paid attention to their synthetic conversions directed toward **1** and **2** (Scheme 5). Debenzylation of **18** was carried out by hydrogenation using Pd/C in dry EtOH at room temperature for 20 min providing the debenzylated product **20** in a quantitative yield. Upon purification using silica gel, compound **20** underwent epimerization at C-5, providing an inseparable mixture of **20** and **21** with a 27 : 73 diasteromeric ratio as determined by ^{1}H NMR analysis. Therefore, after debenzylation, compound **20** was subsequently subjected to the methylation reaction (Me_2SO_4, anhydrous K_2CO_3, acetone, reflux, 1 h). The corresponding γ-butyrolactone **3** together with its diastereomer **4**, which could be easily separated by simple column chromatography, were obtained in 25% and 39% yields, respectively. The stereochemistries of **3** and **4** were confirmed by the NOE experiments (see ESI†). These results implied that epimerization at C-5 of **20** followed by methylation leading to **4** readily took place and competed with a simple methylation to provide **3** (Scheme 6). The observed C-5 epimerization of **20** leading to the thermodynamically more stable **21** was proposed to occur through a lactone ring-opening, facilitated by a hydroxy group on the aromatic ring, to give an intermediate **IV**. Cyclization of the carboxylate intermediate **IV** provided the lactone **21** with *anti*-orientation



Scheme 5 Formal synthesis of (+)-3-*epi*-eupomatilone-6 (**1**) and the 3,5-bis-epimer (**2**).



Scheme 6 Proposed reaction mechanism for the epimerization at C-5 of **20**.

between the methyl group at C-4 and the aromatic ring at C-5 in order to minimize the steric interaction between the two groups. It is worth mentioning that under the reaction conditions, epimerization at C-3 of **20** was not observed. Our synthesized γ-butyrolactones **3** and **4** show the specific optical rotation values of $[\alpha]_D^{27}$ +51.4 (*c* 0.34, $CHCl_3$) {lit.[3i] $[\alpha]_D^{23}$ +57.1 (*c* 0.2, $CHCl_3$)} and $[\alpha]_D^{28}$ +8.3 (*c* 0.35, $CHCl_3$), respectively.

With compounds **3** and **4** in hand, they can be converted to (+)-3-*epi*-eupomatilone-6 (**1**) and the 3,5-bis-epimer (**2**) by following the previously reported studies by Rovis[3i] and Hall,[3e] respectively.

Conclusion

In summary, we accomplished a formal synthesis of (+)-3-*epi*-eupomatilone-6 (**1**) and the 3,5-bis-epimer (**2**). The synthesis scheme involved stereoselective construction of (3*R*,4*S*,5*R*)- and (3*R*,4*S*,5*S*)-trisubstituted γ-butyrolactones **3** and **4** from (2*R*,3*R*)-2,3-dimethyl-4-pentenoic acid derivative **7**. The stereoselective conjugate addition of vinylmagnesium chloride to a chiral α,β-unsaturated *N*-acyl oxazolidinone (Evans' auxiliary) followed by α-methylation was employed to create the *anti*-2,3-dimethyl orientation in (2*R*,3*R*)-**7** leading to the *syn*-3,4-dimethyl relationship present in the target natural molecules.

Experimental

General information

The ^{1}H NMR spectra were recorded on a Bruker DPX-300 (300 MHz), a Bruker-400 (400 MHz) or a Bruker-500 (500 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker DPX-300 (75 MHz) or a Bruker-400 (100 MHz) spectrometer in $CDCl_3$ using residual non-deuterated solvent peaks as an internal standard. The IR spectra were recorded on a Perkin Elmer Spectrum GX FT-IR infrared spectrometer. The mass spectra were recorded using a Thermo Finnigan Polaris Q mass spectrometer. The high resolution mass spectra were recorded on a HR-TOF-MS Micromass model VQ-TOF2 mass spectrometer. Melting points were recorded using a Buchi 510 melting Point Apparatus and are uncorrected. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Dichloromethane (CH_2Cl_2), pentane, and ethanol were distilled over calcium hydride and stored over activated molecular sieves (4 Å). Methanol (MeOH) was distilled over Mg powder. Column chromatography was performed using Merck silica gel 60 (0.063–0.200 mm) (Art 7734). Other common solvents [CH_2Cl_2, hexanes, and ethyl acetate (EtOAc)] were distilled before use.

(*R*,*E*)-3-(But-2-enoyl)-4-phenyloxazolidin-2-one (8b). Compound **8b** was obtained as a white solid according to the reported procedures;[9] mp 75–77 °C (20% CH_2Cl_2 in hexanes); R_f 0.45 (30% EtOAc in hexanes); $[\alpha]_D^{24}$ −143.1 (*c* 1.0, EtOAc) {lit.[9h] $[\alpha]_D^{20}$ −121.2 (*c* 1.0, EtOAc)}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.27 (m, 6H, 5 × Ar*H* and C*H*), 7.17–7.05 (m, 1H, C*H*), 5.50 (dd, *J* = 8.8, 3.9 Hz, 1H, C*H*N), 4.71 (dd, *J* = 8.8, 8.8 Hz, 1H, C*H*H), 4.28 (dd, *J* = 8.8, 3.9 Hz, 1H, CH*H*), 1.95 (dd, *J* = 6.8, 1.5 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.4 (CO), 153.7 (CO), 147.2 (CH), 139.1 (C), 129.1 (2 × CH), 128.6 (CH), 125.8 (2 × CH), 121.7 (CH), 69.9 (CH_2), 57.6 (CH), 18.4 (CH_3). IR ($CHCl_3$): ν_{max} 1780s, 1689s, 1638s, 1385s, 1340s cm^{-1}. MS: *m*/*z* (%) relative intensity 232 [(M + H)$^+$, 26], 211 (24), 172 (100), 159 (30), 144 (25), 117 (27), 104 (31), 91 (36), 77 (27). HRMS (ESI-TOF) calcd for $C_{13}H_{13}NO_3Na$ [M + Na]$^+$: 254.0793, found: 254.0781.

(*R*)-3-[(*S*)-3-Methylpent-4-enoyl]-4-phenyloxazolidin-2-one (9b).[6w] In a glove box, CuBr·SMe_2 (360 mg, 1.76 mmol) was placed in an oven-dried round bottom flask containing a magnetic stirring bar. The flask was sealed with a rubber septum and removed from the glove box. To the reaction flask, dry THF (6 mL) and SMe_2 (3 mL) were added under argon, and the resulting yellow solution was cooled at −40 °C. Vinylmagnesium chloride (1.6 M in THF, 4.4 mL, 7.0 mmol) was then added dropwise to give a dark green suspension. After stirring at −40 °C for 10 min, a solution of **8b** (463 mg, 2.0 mmol) in dry THF (6 mL) was added as rapidly as possible, and the resulting dark brown solution was vigorously stirred for 5 min. The reaction mixture was then quenched at −40 °C with a saturated aqueous NH_4Cl solution (5 mL), followed by the addition of 30% (v/v) aqueous ammonia solution (5 mL). After stirring for 30 min at room temperature, the resulting solution was diluted with brine. The organic phase was then collected, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (30% EtOAc in hexanes) provided **9b** as a colorless solid (444 mg, 86% yield, dr = 90 : 10 as determined by 500 MHz ^{1}H NMR analysis). Recrystallization (10% CH_2Cl_2 in hexanes) yielded **9b**[6q,y] (320 mg, 62% yield) with a 98 : 2 diastereomeric ratio. mp 59–61 °C (10% CH_2Cl_2 in hexanes); R_f 0.54 (30% EtOAc in hexanes); $[\alpha]_D^{24}$ −62.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43–7.28 (m, 5H, 5 × Ar*H*), 5.78 (ddd, *J* = 17.2, 10.6, 7.0 Hz, 1H, C*H*), 5.46 (dd, *J* = 8.7, 3.7 Hz, 1H, C*H*N), 4.99–4.90 (m, 2H, CH_2), 4.71 (dd, *J* = 8.8, 8.8 Hz, 1H, C*H*H), 4.30 (dd, *J* = 8.8, 3.7 Hz, 1H, CH*H*), 3.12 (dd, *J* = 15.9, 6.6 Hz, 1H, C*H*H), 2.87 (dd, *J* = 15.9, 7.4 Hz, 1H, CH*H*), 2.79–2.69 (m, 1H, C*H*), 1.04 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5 (CO), 153.7 (CO), 142.4 (CH), 139.0 (C), 129.1 (2 × CH), 128.7 (CH), 126.0 (2 × CH), 113.4 (CH_2), 69.9 (CH_2), 57.6 (CH), 41.8 (CH_2), 33.8 (CH), 19.6 (CH_3). IR (KBr): ν_{max} 1772s, 1705s, 1386s, 1364m, 1309s, 1196s cm^{-1}. MS: *m*/*z* (%) relative intensity 260 [(M + H)$^+$, 100], 121 (19), 104 (15), 96 (21), 82 (15). HRMS (ESI-TOF) calcd for $C_{15}H_{17}NO_3Na$ [M + Na]$^+$: 282.1106, found: 282.1105.

Compound 10. A pale yellow solid; mp 64–66 °C (30% EtOAc in hexanes); R_f 0.35 (30% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, major isomer): δ 7.27–7.09 (m, 5H, 5 × Ar*H*), 5.83–5.69 (m, 1H, C*H*), 5.69–5.58 (m, 1H, C*H*), 5.58–5.45 (m, 1H, O*H*), 5.05–4.83 (m, 4H, 2 × CH_2), 4.45–4.32 (m, 1H, C*H*N), 4.05–3.95 (m, 2H, CH_2), 2.86–2.77 (m, 1H, C*H*H), 2.77–2.68 (m, 1H, CH*H*), 2.60–2.50 (m, 1H, C*H*), 2.44–2.36 (m, 2H, CH_2), 2.36–2.29 (m, 2H, CH_2), 2.18–1.95 (m, 2H, CH_2), 0.94 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, major isomer): δ 173.0 (CO), 171.3 (CO), 142.6 (CH), 136.9 (C), 136.6 (CH), 129.2 (2 × CH), 128.6 (2 × CH), 126.8 (CH), 115.7 (CH_2), 113.5 (CH_2), 64.7 (CH_2), 49.4 (CH), 43.8 (CH_2), 37.6 (CH_2), 34.7 (CH), 33.4 (CH_2), 28.8 (CH_2), 19.6 (CH_3). IR (KBr): ν_{max} 3293s, 1726s, 1648s, 1552s, 1190m, 918m cm^{-1}. MS: *m*/*z* (%) relative intensity 329 (M$^+$, 12), 237 (17), 230 (13), 178 (17), 156 (13), 138 (30), 91 (81), 77 (30). HRMS (ESI-TOF) calcd for $C_{20}H_{27}NO_3Na$ [M + Na]$^+$: 352.1889, found: 352.1902.

(*R*)-3-[(2*R*,3*R*)-2,3-Dimethylpent-4-enoyl]-4-phenyloxazolidin-2-one (7). A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum

was charged with hexamethyldisilazane (HMDS) (0.5 mL, 2.1 mmol) and dry THF (5 mL). The solution was cooled at −78 °C and then a solution of *n*-BuLi (1.64 M in hexanes, 1.1 mL, 1.8 mmol) was added dropwise. After stirring at −78 °C for 1 h, a solution of **9b** (dr = 98 : 2, 518 mg, 2.0 mmol) in dry THF (3 mL) was added dropwise, and the reaction mixture was stirred at −78 °C for 1 h. To the resulting lithium enolate solution, MeI (0.24 mL, 4.0 mmol) was then added dropwise. The reaction mixture was slowly warmed up to 0 °C over 3 h, and the stirring was continued at 0 °C for 2 h. Then it was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 25 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (30% EtOAc in hexanes) gave **7** as a colorless oil (437 mg, 80% yield, dr = 98 : 2 as determined by 400 MHz ^{1}H NMR analysis). R_f 0.66 (30% EtOAc in hexanes); $[\alpha]_D^{23}$ −89.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.17 (m, 5H, 5 × Ar*H*), 5.66–5.55 (m, 1H, C*H*), 5.36 (dd, *J* = 8.8, 3.5 Hz, 1H, C*H*N), 4.98–4.90 (m, 2H, CH_2), 4.60 (dd, *J* = 8.8, 8.8 Hz, 1H, C*H*H), 4.17 (dd, *J* = 8.8, 3.5 Hz, 1H, CH*H*), 3.65 (dq, *J* = 7.0, 7.0 Hz, 1H, C*H*), 2.41 (dq, *J* = 14.9, 7.0 Hz, 1H, C*H*), 0.96 (d, *J* = 7.0 Hz, 6H, 2 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8 (CO), 153.4 (CO), 140.8 (CH), 139.2 (C), 129.2 (2 × CH), 128.6 (CH), 125.6 (2 × CH), 115.2 (CH_2), 69.7 (CH_2), 57.7 (CH), 42.4 (CH), 40.6 (CH), 18.7 (CH_3), 15.2 (CH_3). IR (neat): ν_{max} 1781s, 1704s, 1456m, 1383s, 1319s, 1199s cm^{-1}. MS: *m*/*z* (%) relative intensity 274 [$(M + H)^+$, 74], 258 (24), 218 (32), 200 (24), 164 (21), 146 (40), 120 (69), 104 (100), 95 (61), 77 (62). HRMS (ESI-TOF) calcd for $C_{16}H_{19}NO_3Na$ $[M + Na]^+$: 296.1263, found: 296.1263.

(2*R*,3*R*)-2,3-Dimethyl-4-pentenoic acid (11).[4b,f] A solution of **7** (dr = 98 : 2, 235 mg, 0.9 mmol) in a 1 : 1 mixture of THF and water (12 mL) cooled at 0 °C was treated with an aqueous 30% solution of H_2O_2 (0.39 mL, 3.4 mmol) and $LiOH{\cdot}H_2O$ (70 mg, 1.7 mmol). After stirring at 0 °C for 2 h, two phases of the reaction mixture were separated. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give the recovered chiral auxiliary in 83% yield (117 mg). The aqueous phase was acidified (pH 1) by using 1 M HCl and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (20% EtOAc in hexanes) gave **11** (100 mg, 91% yield, dr = 98 : 2 as determined by 400 MHz ^{1}H NMR analysis) as a colorless liquid. R_f 0.30 (20% EtOAc in hexanes); $[\alpha]_D^{24}$ +37.8 (*c* 1.19, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.59 (ddd, *J* = 17.2, 10.3, 8.2 Hz, 1H, C*H*), 5.04–4.93 (m, 2H, CH_2), 2.40 (dq, *J* = 14.7, 7.1 Hz, 1H, C*H*), 2.27 (dq, *J* = 7.1, 7.1 Hz, 1H, C*H*), 1.06 (d, *J* = 7.1 Hz, 3H, CH_3), 1.00 (d, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.6 (CO), 140.5 (CH), 115.3 (CH_2), 44.9 (CH), 40.8 (CH), 18.3 (CH_3), 14.3 (CH_3). IR (neat): ν_{max} 3081s, 1707s, 1460m, 1419m, 1289m, 1220m, 917m cm^{-1}. MS: *m*/*z* (%) relative intensity 129 [$(M + H)^+$, 20], 128 (M^+, 8), 113 (40), 83 (49), 67 (53).

***tert*-Butyl{[(2*R*,3*R*)-2,3-dimethylpent-4-en-1-yl]oxy}dimethylsilane (12).** A solution of $LiBH_4$ (231 mg, 10 mmol) in dry THF (13 mL) was added to a solution of **7** (dr = 98 : 2, 1.23 g, 4.5 mmol) in dry THF (18 mL) in the presence of MeOH (0.5 mL) cooled at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h, then carefully quenched with an aqueous NaOH solution (1 M, 10 mL) and extracted with Et_2O (3 × 30 mL). The combined organic phase was dried over anhydrous Na_2SO_4. Purification by column chromatography (70% Et_2O in pentane) gave the corresponding alcohol as a colorless liquid (354 mg, 69% yield) and the recovered chiral auxiliary as a white solid (529 mg, 72% yield). The obtained alcohol was dissolved in dry CH_2Cl_2 (6 mL) and then imidazole (530 mg, 6.2 mmol) and a solution of TBSCl (1.0 g, 6.2 mmol) in dry hexanes (0.9 mL) were added. The reaction mixture was allowed to stir at room temperature overnight and then quenched with a saturated aqueous $NaHCO_3$ solution (10 mL). The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (10% Et_2O in pentane) gave **12** as a colorless liquid (687 mg, 97% yield, dr = 98 : 2 as determined by 400 MHz ^{1}H NMR analysis). R_f 0.80 (10% Et_2O in pentane); $[\alpha]_D^{24}$ +21.2 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75–5.66 (m, 1H, C*H*), 5.00–4.91 (m, 2H, CH_2), 3.49 (dd, *J* = 9.8, 6.5 Hz, 1H, C*H*H), 3.39 (dd, *J* = 9.8, 6.5 Hz, 1H, CH*H*), 2.35–2.26 (m, 1H, C*H*), 1.61–1.52 (m, 1H, C*H*), 1.00 (d, *J* = 6.9 Hz, 3H, CH_3), 0.89 [s, 9H, $SiC(CH_3)_3$], 0.81 (d, *J* = 6.9 Hz, 3H, CH_3), 0.03 (s, 6H, 2 × $SiCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8 (CH), 113.9 (CH_2), 66.3 (CH_2), 40.5 (CH), 38.8 (CH), 25.9 (3 × CH_3), 18.4 (C), 17.9 (CH_3), 12.9 (CH_3), −5.4 (2 × CH_3). IR ($CHCl_3$): ν_{max} 1472w, 1257m, 1091m, 838s cm^{-1}. MS: *m*/*z* (%) relative intensity 229 [$(M + H)^+$, 2], 220 (100), 204 (53), 190 (85), 148 (76), 98 (32). HRMS (ESI-TOF) calcd for $C_{13}H_{29}OSi$ $[M + H]^+$: 229.1988, found: 229.1986.

(1*R*,2*S*,3*R*)-1-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-4-[(*tert*-butyldimethylsilyl)oxy]-2,3-dimethylbutan-1-ol (5) and (1*S*,2*S*,3*R*)-1-[4-(benzyloxy)-3,5-dimethoxyphenyl]-4-[(*tert*-butyldimethylsilyl)oxy]-2,3-dimethylbutan-1-ol (6). To a solution of **12** (dr = 98 : 2, 457 mg, 2.0 mmol) and NMO (812 mg, 6.0 mmol) in CH_2Cl_2 (80 mL) were added OsO_4 (2.5% w/v in *t*-butanol, 1 mL, 0.1 mmol) and water (1 mL). After stirring for 10 h at room temperature, $NaIO_4$ (852 mg, 4.0 mmol) was added, and stirring of the reaction mixture continued for 30 min. Then it was quenched with a saturated aqueous $Na_2S_2O_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The crude mixture was filtered through a short column (50% Et_2O in pentane) to give **13**. A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with 2-(benzyloxy)-5-bromo-1,3-dimethoxybenzene (986 mg, 3.0 mmol) and dry THF (5 mL). The solution was cooled at −78 °C and then a solution of *n*-BuLi (1.77 M in hexanes, 1.70 mL, 3.0 mmol) was added dropwise. The resulting mixture was stirred for 10 min and then a solution of **13** in dry THF (5 mL) was added dropwise. After stirring at −78 °C for 2 h, the reaction mixture was quenched with a saturated

aqueous NH_4Cl solution and extracted with EtOAc (3 × 30 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (20% EtOAc in hexanes) gave **5** (446 mg, 47% yield) and **6** (209 mg, 22% yield).

5: a colorless oil; R_f 0.34 (20% EtOAc in hexanes); $[\alpha]_D^{22}$ +20.1 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 6.9 Hz, 2H, 2 × Ar*H*), 7.21–7.12 (m, 3H, 3 × Ar*H*), 6.46 (s, 2H, 2 × Ar*H*), 4.85 (s, 2H, CH_2), 4.66 (s, 1H, C*H*), 4.42 (br s, 1H, O*H*), 3.69 (s, 6H, 2 × OCH_3), 3.45 (dd, *J* = 10.3, 9.9 Hz, 1H, C*H*H), 3.35 (dd, *J* = 10.3, 4.0 Hz, 1H, CH*H*), 1.94–1.88 (m, 1H, C*H*), 1.68–1.63 (m, 1H, C*H*), 0.81 [s, 9H, SiC(CH_3)$_3$], 0.79 (d, *J* = 7.3 Hz, 3H, CH_3), 0.61 (d, *J* = 7.3 Hz, 3H, CH_3), 0.00 (s, 6H, 2 × SiCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1 (2 × C), 140.5 (C), 138.1 (C), 135.4 (C), 128.5 (2 × CH), 128.1 (2 × CH), 127.7 (CH), 103.2 (2 × CH), 77.1 (CH), 75.0 (CH_2), 65.0 (CH_2), 56.1 (2 × CH_3), 46.0 (CH), 40.4 (CH), 25.9 (3 × CH_3), 18.4 (C), 17.5 (CH_3), 5.6 (CH_3), −5.4 (CH_3), −5.5 (CH_3). IR ($CHCl_3$): ν_{max} 3357w, 1592m, 1505m, 1464m, 1418m 1131s, 1068m, 837w cm^{-1}. MS: *m*/*z* (%) relative intensity 476 [$(M + H)^+$, 1], 271 (19), 251 (39), 223 (41), 218 (35), 191 (25), 181 (27), 152 (33), 91 (100), 77 (31). HRMS (ESI-TOF) calcd for $C_{27}H_{42}O_5SiNa$ $[M + Na]^+$: 497.2699, found: 497.2701.

6: a colorless oil; R_f 0.41 (20% EtOAc in hexanes); $[\alpha]_D^{22}$ −14.8 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.0 Hz, 2H, 2 × Ar*H*), 7.23–7.10 (m, 3H, 3 × Ar*H*), 6.42 (s, 2H, 2 × Ar*H*), 4.85 (s, 2H, CH_2), 4.44 (d, *J* = 5.8 Hz, 1H, O*H*), 4.30 (dd, *J* = 5.8, 5.8 Hz, 1H, C*H*), 3.68 (s, 6H, 2 × OCH_3), 3.45 (dd, *J* = 10.1, 9.0 Hz, 1H, C*H*H), 3.36 (dd, *J* = 10.1, 3.6 Hz, 1H, CH*H*), 1.98–1.87 (m, 1H, C*H*), 1.86–1.76 (m, 1H, C*H*), 0.82 [s, 9H, SiC(CH_3)$_3$], 0.72 (d, *J* = 7.4 Hz, 3H, CH_3), 0.70 (d, *J* = 7.4 Hz, 3H, CH_3), 0.00 (s, 6H, 2 × SiCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3 (2 × C), 140.8 (C), 138.0 (C), 135.7 (C), 128.5 (2 × CH), 128.1 (2 × CH), 127.7 (CH), 103.6 (2 × CH), 77.0 (CH), 75.0 (CH_2), 65.6 (CH_2), 56.1 (2 × CH_3), 44.9 (CH), 35.1 (CH), 25.9 (3 × CH_3), 18.3 (C), 15.7 (CH_3), 12.7 (CH_3), −5.5 (CH_3), −5.6 (CH_3). IR ($CHCl_3$): ν_{max} 3337w, 1593m, 1506m, 1464m, 1419m, 1259m, 1130s, 1066m, 839s cm^{-1}. MS: *m*/*z* (%) relative intensity 475 (M^+, 1), 363 (24), 334 (21), 304 (21), 273 (15), 251 (16), 247 (37), 232 (100), 218 (77), 201 (25), 188 (49), 91 (51). HRMS (ESI-TOF) calcd for $C_{27}H_{42}O_5SiNa$ $[M + Na]^+$: 497.2699, found: 497.2697.

An alternative method to synthesize compound 6. MnO_2 (260 mg, 3.0 mmol) was added to a solution of a 2 : 1 mixture of **5** and **6** (47 mg, 0.1 mmol) in dry pentane (1 mL) at room temperature. The resulting black suspension was stirred for 13 h, filtered through a Celite pad, and the residue was eluted with EtOAc (50 mL). Purification by column chromatography (100% CH_2Cl_2) gave the corresponding ketone in 89% yield (42 mg) as a colorless oil. R_f 0.62 (100% CH_2Cl_2); $[\alpha]_D^{22}$ +39.5 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.1 Hz, 2H, 2 × Ar*H*), 7.35–7.22 (m, 3H, 3 × Ar*H*), 7.20 (s, 2H, 2 × Ar*H*), 5.07 (s, 2H, CH_2), 3.85 (s, 6H, 2 × OCH_3), 3.64 (dd, *J* = 10.0, 4.9 Hz, 1H, C*H*H), 3.58–3.48 (m, 2H, CH*H* and C*H*), 2.04–1.90 (m, 1H, C*H*), 1.15 (d, *J* = 6.9 Hz, 3H, CH_3), 0.91 (d, *J* = 6.8 Hz, 3H, CH_3), 0.87 [s, 9H, SiC(CH_3)$_3$], 0.02 (s, 3H, SiCH_3), 0.00 (s, 3H, SiCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.7 (CO), 153.4 (2 × C), 141.3 (C), 137.4 (C), 133.0 (C), 128.4 (2 × CH), 128.2 (2 × CH), 128.0 (CH), 105.8 (2 × CH), 75.0 (CH_2), 65.0 (CH_2), 56.2 (2 × CH_3), 41.5 (CH), 38.8 (CH), 25.9 (3 × CH_3), 18.3 (C), 15.9 (CH_3), 15.4 (CH_3), −5.4 (CH_3), −5.5 (CH_3). IR ($CHCl_3$): ν_{max} 1671s, 1584s, 1501m, 1464s, 1415s, 1322s, 1131s, 838s cm^{-1}. MS: *m*/*z* (%) relative intensity 415 (100), 383 (5), 324 (18), 306 (9), 209 (15), 91 (40). HRMS (ESI-TOF) calcd for $C_{27}H_{40}O_5SiNa$ $[M + Na]^+$: 495.2543, found: 495.2546.

A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with the above obtained ketone (47 mg, 0.1 mmol) and dry MeOH (1.2 mL). $NaBH_4$ (38 mg, 1 mmol) was added at −78 °C, and the resulting white suspension was allowed to warm to 0 °C over 3 h and then stirred at 0 °C for an additional 1 h. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (100% CH_2Cl_2) gave **6** (42 mg, 89% yield) as a single diastereomer as determined by ^1H NMR (400 MHz) analysis.

(2*S*,3*S*,4*R*)-3,4-Dimethyl-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran (16). According to the same procedure as for **5** and **6**, oxidative cleavage of **12** (dr = 98 : 2, 457 mg, 2.0 mmol) provided **13**, which was further reacted with (3,4,5-trimethoxyphenyl)lithium (**14**) [prepared from 5-bromo-1,2,3-trimethoxybenzene (741 mg, 3.0 mmol) and *n*-BuLi (1.77 M in hexanes, 1.70 mL, 3.0 mmol)] at −78 °C for 2 h. Purification by column chromatography (30% EtOAc in hexanes) gave a colorless oil of **16** (223 mg, 42% yield) as a single diastereomer as determined by ^1H NMR (400 MHz) analysis. R_f 0.45 (30% EtOAc in hexanes); $[\alpha]_D^{28}$ +29.2 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.54 (s, 2H, 2 × Ar*H*), 4.37 (d, *J* = 7.9 Hz, 1H, C*H*), 4.25 (dd, d, *J* = 8.3, 6.5 Hz, 1H, C*H*H), 3.87 (s, 6H, 2 × OCH_3), 3.83 (s, 3H, OCH_3), 3.63 (dd, *J* = 8.3, 4.8 Hz, 1H, CH*H*), 2.46–2.34 (m, 1H, C*H*), 2.11 (dq, *J* = 14.4, 6.9 Hz, 1H, C*H*), 1.01 (d, *J* = 6.9 Hz, 3H, CH_3), 1.00 (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2 (2 × C), 138.6 (2 × C), 102.8 (2 × CH), 86.7 (CH), 75.3 (CH_2), 60.8 (CH_3), 56.1 (2 × CH_3), 45.3 (CH), 36.7 (CH), 13.4 (CH_3), 12.1 (CH_3). IR ($CHCl_3$): ν_{max} 1593m, 1508m, 1464m, 1421m, 1330m, 1234m, 1128s cm^{-1}. MS: *m*/*z* (%) relative intensity 266 (M^+, 100), 235 (31), 196 (64), 181 (59). HRMS (ESI-TOF) calcd for $C_{15}H_{22}O_4Na$ $[M + Na]^+$: 289.1416, found: 289.1427.

(3*R*,4*S*,5*R*)-5-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-3,4-dimethyldihydrofuran-2(3*H*)-one (18). A solution of TBAF (30 mg, 0.1 mmol) in dry THF (5 mL) was added to a solution of **5** (48 mg, 0.1 mmol) in dry THF (1 mL) at 25 °C under argon. After stirring for 2 h, the reaction mixture was diluted and extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4. The obtained crude product was dissolved in dry CH_2Cl_2 (1 mL) under argon and then DIB (103 mg, 0.3 mmol) and TEMPO (3 mg, 0.02 mmol) were sequentially added at room temperature. After stirring for 3.5 h, the resulting suspension was quenched with a saturated aqueous $Na_2S_2O_3$ solu-

tion (5 mL) and diluted with EtOAc (5 mL). The organic phase was collected and then washed with a saturated aqueous $NaHCO_3$ solution and water. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (30% EtOAc in hexanes) afforded a pale yellow solid of **18** (30 mg, 83% yield) as a single diastereomer as determined by ^{1}H NMR (400 MHz) analysis. mp 75–77 °C (10% CH_2Cl_2 in hexanes); R_f 0.40 (30% EtOAc in hexanes); $[\alpha]_D^{25}$ +50.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.4 Hz, 2H, 2 × Ar*H*), 7.30–7.16 (m, 3H, 3 × Ar*H*), 6.39 (s, 2H, 2 × Ar*H*), 5.38 (d, *J* = 5.0 Hz, 1H, C*H*), 4.94 (s, 2H, CH_2), 3.74 (s, 6H, 2 × OCH_3), 2.95–2.70 (m, 1H, C*H*), 2.75–2.60 (m, 1H, C*H*), 1.15 (d, *J* = 7.2 Hz, 3H, CH_3), 0.49 (d, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9 (CO), 153.7 (2 × C), 137.7 (C), 136.1 (C), 132.0 (C), 128.5 (2 × CH), 128.1 (2 × CH), 127.8 (CH), 102.1 (2 × CH), 82.2 (CH), 74.9 (CH_2), 56.2 (2 × CH_3), 41.1 (CH), 40.1 (CH), 10.1 (CH_3), 9.3 (CH_3). IR ($CHCl_3$): ν_{max} 1772s, 1594s, 1506m, 1463s, 1421m, 1363m, 1339m, 1175s, 1132s, 970m cm^{-1}. MS: *m*/*z* (%) relative intensity 356 (M^+, 2), 264 (100), 209 (48), 181 (11), 177 (19), 91 (22). HRMS (ESI-TOF) calcd for $C_{21}H_{24}O_5Na$ $[M + Na]^+$: 379.1521, found: 379.1521.

(3*R*,4*S*,5*S*)-5-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-3,4-dimethyldihydrofuran-2(3*H*)-one (19). According to the same procedure as for **18**, desilylation of **6** (95 mg, 0.2 mmol) followed by oxidative lactonization of the crude product using DIB (186 mg, 0.6 mmol) and TEMPO (6 mg, 0.04 mmol), and purification by column chromatography (30% EtOAc in hexanes) provided a pale yellow solid of **19** (57 mg, 80% yield) with contamination of its C-3 epimer (dr = 95 : 5) as determined by ^{1}H NMR (400 MHz) analysis. mp 79–81 °C (10% CH_2Cl_2 in hexanes); R_f 0.55 (30% EtOAc in hexanes); $[\alpha]_D^{22}$ +14.0 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.6 Hz, 2H, 2 × Ar*H*), 7.35–7.15 (m, 3H, 3 × Ar*H*), 6.43 (s, 2H, 2 × Ar*H*), 4.93 (s, 2H, CH_2), 4.91 (d, *J* = 6.7 Hz, 1H, C*H*), 3.75 (s, 6H, 2 × OCH_3), 2.73 (dq, *J* = 7.4, 7.4 Hz, 1H, C*H*), 2.47 (dq, *J* = 14.3, 7.4 Hz, 1H, C*H*), 1.16 (d, *J* = 7.4 Hz, 3H, CH_3), 1.04 (d, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7 (CO), 153.8 (2 × C), 137.7 (C), 136.9 (C), 134.1 (C), 128.5 (2 × CH), 128.2 (2 × CH), 127.9 (CH), 102.6 (2 × CH), 85.8 (CH), 75.0 (CH_2), 56.3 (2 × CH_3), 42.3 (CH), 38.3 (CH), 12.7 (CH_3), 10.2 (CH_3). IR ($CHCl_3$): ν_{max} 1769s, 1594m, 1507m, 1464m, 1132s cm^{-1}. MS: *m*/*z* (%) relative intensity 356 (M^+, 19), 265 (100), 209 (58), 181 (25), 177 (26), 149 (14), 91 (70). HRMS (ESI-TOF) calcd for $C_{21}H_{24}O_5Na$ $[M + Na]^+$: 379.1521, found: 379.1537.

(3*R*,4*S*,5*R*)-3,4-Dimethyl-5-(3,4,5-trimethoxyphenyl)dihydrofuran-2(3*H*)-one (3)[3i] and (3*R*,4*S*,5*S*)-3,4-dimethyl-5-(3,4,5-trimethoxyphenyl)dihydrofuran-2(3*H*)-one (4). A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with **18** (36 mg, 0.1 mmol), Pd/C (10% w/w, 11 mg, 0.1 mmol), and dry EtOH (2.5 mL). The argon inlet was replaced by a H_2 balloon, and the reaction mixture was stirred at room temperature for 20 min. The resulting mixture was filtered through a Celite pad and then the residue was eluted with EtOAc (25 mL) to yield **20** in a quantitative yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.48 (s, 2H, 2 × Ar*H*), 5.45 (d, *J* = 5.0 Hz, 1H, C*H*), 3.87 (s, 6H, 2 × OCH_3), 2.99 (dq, *J* = 7.2, 7.2 Hz, 1H, C*H*), 2.80–2.77 (m, 1H, C*H*), 1.21 (d, *J* = 7.2 Hz, 3H, CH_3), 0.56 (d, *J* = 7.2 Hz, 3H, CH_3).

Compound **20** was dissolved in dry acetone (1 mL) and then Me_2SO_4 (30 μL, 0.4 mmol) and anhydrous K_2CO_3 (69 mg, 0.5 mmol) were added. After stirring at reflux for 1 h, the reaction mixture was cooled to room temperature, quenched with water, and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. Purification by column chromatography (10% EtOAc in hexanes) gave **3** (7 mg, 25% yield) and **4** (11 mg, 39% yield).

3: a colorless viscous oil; R_f 0.25 (30% EtOAc in hexanes); $[\alpha]_D^{27}$ +51.4 (*c* 0.34, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.48 (s, 2H, 2 × Ar*H*), 5.46 (d, *J* = 4.9 Hz, 1H, C*H*), 3.86 (s, 6H, 2 × OCH_3), 3.85 (s, 3H, OCH_3), 3.00 (dq, *J* = 7.2, 7.2 Hz, 1H, C*H*), 2.82–2.72 (m, 1H, C*H*), 1.22 (d, *J* = 7.2 Hz, 3H, CH_3), 0.58 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9 (CO), 153.5 (2 × C), 137.4 (C), 131.9 (C), 102.1 (2 × CH), 82.2 (CH), 60.9 (CH_3), 56.2 (2 × CH_3), 41.2 (CH), 40.1 (CH), 10.1 (CH_3), 9.4 (CH_3). IR ($CHCl_3$): ν_{max} 1771s, 1594m, 1464m, 1173m, 1131s cm^{-1}. MS: *m*/*z* (%) relative intensity 280 (M^+, 58), 205 (11), 196 (100), 181 (36), 180 (12). HRMS (ESI-TOF) calcd for $C_{15}H_{20}O_5Na$ $[M + Na]^+$: 303.1208, found: 303.1207.

4: a colorless viscous oil; R_f 0.35 (30% EtOAc in hexanes); $[\alpha]_D^{28}$ +8.3 (*c* 0.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.51 (s, 2H, 2 × Ar*H*), 4.98 (d, *J* = 6.6 Hz, 1H, C*H*), 3.86 (s, 6H, 2 × OCH_3), 3.84 (s, 3H, OCH_3), 2.79 (dq, *J* = 7.4, 7.4 Hz, 1H, C*H*), 2.53 (dq, *J* = 14.1, 7.4 Hz, 1H, C*H*), 1.23 (d, *J* = 7.4 Hz, 3H, CH_3), 1.11 (d, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6 (CO), 153.5 (2 × C), 137.9 (C), 134.0 (C), 102.5 (2 × CH), 85.7 (CH), 60.9 (CH_3), 56.2 (2 × CH_3), 42.3 (CH), 38.3 (CH), 12.7 (CH_3), 10.2 (CH_3). IR ($CHCl_3$): ν_{max} 1770s, 1594m, 1509m, 1464m, 1421m, 1239m, 1131s, 1002m cm^{-1}. MS: *m*/*z* (%) relative intensity 280 (M^+, 58), 279 (41), 205 (21), 196 (100), 181 (59), 178 (40). HRMS (ESI-TOF) calcd for $C_{15}H_{20}O_5Na$ $[M + Na]^+$: 303.1208, found: 303.1206.

(3*R*,4*S*,5*S*)-5-(2-Bromo-3,4,5-trimethoxyphenyl)-3,4-dimethyldihydrofuran-2(3*H*)-one (22).[3e] To a solution of **4** (25 mg, 0.09 mmol) in $CHCl_3$ (1 mL) was added NBS (17 mg, 0.1 mmol) at room temperature. After stirring for 1.5 h, the solvent was removed *in vacuo*, and the crude product was purified by column chromatography (30% EtOAc in hexanes) to give a colorless oil of **22** (29 mg, 90% yield) as a single diastereomer as determined by ^{1}H NMR (400 MHz) analysis. R_f 0.43 (30% EtOAc in hexanes); $[\alpha]_D^{27}$ −18.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.63 (s, 1H, Ar*H*), 5.34 (d, *J* = 2.2 Hz, 1H, C*H*), 3.92 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 2.75 (dq, *J* = 7.4, 7.4 Hz, 1H, C*H*), 2.63–2.55 (m, 1H, C*H*), 1.25 (d, *J* = 7.4 Hz, 3H, CH_3), 1.19 (d, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.8 (CO), 153.1 (C), 151.2 (C), 142.7 (C), 133.9 (C), 107.4 (C), 104.7 (CH), 84.3 (CH), 61.1 (2 × CH_3), 56.3 (CH_3), 41.1 (CH), 36.4 (CH), 14.3 (CH_3), 9.6 (CH_3). IR ($CHCl_3$): ν_{max} IR ($CHCl_3$): ν_{max} 1773s, 1571m, 1484m, 1397s, 1331s, 1167s, 1111s, 999s cm^{-1}. MS: *m*/*z* (%) relative intensity 359

(M^+, 32), 358 (42), 357 (38), 276 (100), 275 (58), 274 (98), 273 (76), 259 (22), 204 (13), 124 (19). HRMS (ESI-TOF) calcd for $C_{15}H_{19}O_5BrNa$ $[M + Na]^+$: 381.0314, found: 381.0310.

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