Tetrahedron 71 (2015) 4779–4787

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A model study on installation of (*Z*)-γ-methylglutaconic acid onto the 3-aminophenol core of divergolide A

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ARTICLE INFO

Article history:
Received 10 April 2015
Received in revised form 12 May 2015
Accepted 15 May 2015
Available online 22 May 2015

Keywords:
Alkene
Amidation
Aminophenol
Carboxylic acid
Divergolide A
Isomerization

ABSTRACT

Divergolide A and its four congeners, divergolide E–H, possess an amido-substituted hydroquinone core, which is biosynthetically transformed from an aromatic starter unit, 3-amino-5-hydroxybenzoic acid (AHBA). The macrocyclic ring of divergolide A and F is assembled by linking the amido hydroquinone unit with the polyketide backbone through (*Z*)-γ-methylglutaconic acid as the tether while (*E*)-γ-methylglutaconic acid is found in divergolide E, G, and H. A model study has been conducted for installation of (*Z*)-γ-methylglutaconic acid onto the 3-aminophenol core of divergolide A via two methods: (a) the CuI–MeNHCH$_2$CH$_2$NHMe-catalyzed amidation of methyl (*Z*)-4-carbamoyl-2-methylbut-2-enoate with an aryl bromide; and (b) regioselective aminolysis of (*Z*)-γ-methylglutaconic anhydride with an aniline derivative. Isomerization of the (*Z*)-configuration under the CuI catalysis conditions was observed to give mainly the (*E*)-product while (*Z*)-product was obtained exclusively under the aminolysis conditions. These results might be useful for total synthesis of divergolide A and E–H.

1. Introduction

Divergolides are a family of intriguing ansamycins (with some related derivatives) produced by the endophytic strains isolated from the stem of mangrove trees.[1] The strain *Streptomyces* sp. HKI0576 from *Bruguiera gymnorrhiza*, one of the dominant mangrove species along the Chinese coast, produced divergolide A–I and L–N[2–4] while the strain *Streptomyces* sp. HKI0595 from *Kandelia candel*,[5] a widespread mangrove tree found in southern India, southeast China and southern Japan, produced divergolide J and K.[4] The structure of divergolide A (**1**, Fig. 1), as confirmed by X-ray crystal structural analysis,[2] features a 1-amino-3-hydroxybenzene core, a bridged acetal subunit, and a macrocyclic ring. The latter is assembled from the disrupted polyketide backbone and the aminophenol core through (*Z*)-γ-methylglutaconic acid as the tether. Divergolide A has four congeners, divergolide E–H (structures not shown)[3], which are the diastereomers with C3″-(*E*)-configuration (divergolide E), epimeric C2–Me (divergolide F), both C3″-(*E*)-configuration and epimeric C2–Me (divergolide G), and both C3″-(*E*)-configuration and an expanded macrolactone ring at C12–OH (divergolide H), respectively. Moreover, divergolide I–L are the congeners of divergolide C while divergolide M and N are the biosynthetic intermediates prematurely released from the modular assembly line.[4] Hertweck and co-workers proposed a revised model for polyketide diversification in the divergolide biosynthesis pathway,[2,3] suggesting formation of divergolides from a common precursor similar to the structure **2** with a C2″-(*E*)-double bond instead of the C3″-(*E*)-double bond as shown in **2**. Divergolide A–D were reported to exhibit strong activity against *Bacillus subtilis*, *Mycobacterium vaccae*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus faecalis*.[2] Also, divergolide D delivered pronounced anticancer activity with a mean IC$_{50}$ value of 2.4 μM against a panel of 40 tumor cell lines including the most sensitive cell lines (IC$_{50}$ values of 1.0–2.0 μM) such as lung cancer (LXFA 629L), pancreatic cancer (PANC-1), renal cancer (RXF 486L), and sarcoma (Saos-2).[2] The biological activity of divergolide A and D renders them as the potential candidates for further development as anti-infectives and anticancer agents, respectively. We[6] and others[7,8] have disclosed studies on the total synthesis of divergolide A, C, and D. In our previous work,[6] a ring-closing metathesis (RCM) strategy was envisioned to assemble the macrocyclic ring and synthesis of a simplified amido hydroquinone core and the C10–C15 diene fragment **5**[8] was achieved. We report here on the model study toward installation of (*Z*)-γ-methylglutaconic acid onto the 3-aminophenol core of divergolide A.

2. Results and discussion

According to the proposed divergolide biosynthetic pathway by Hertweck,[2,3] the C2 configuration of divergolide A (**1**, Fig. 1) was

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http://dx.doi.org/10.1016/j.tet.2015.05.052
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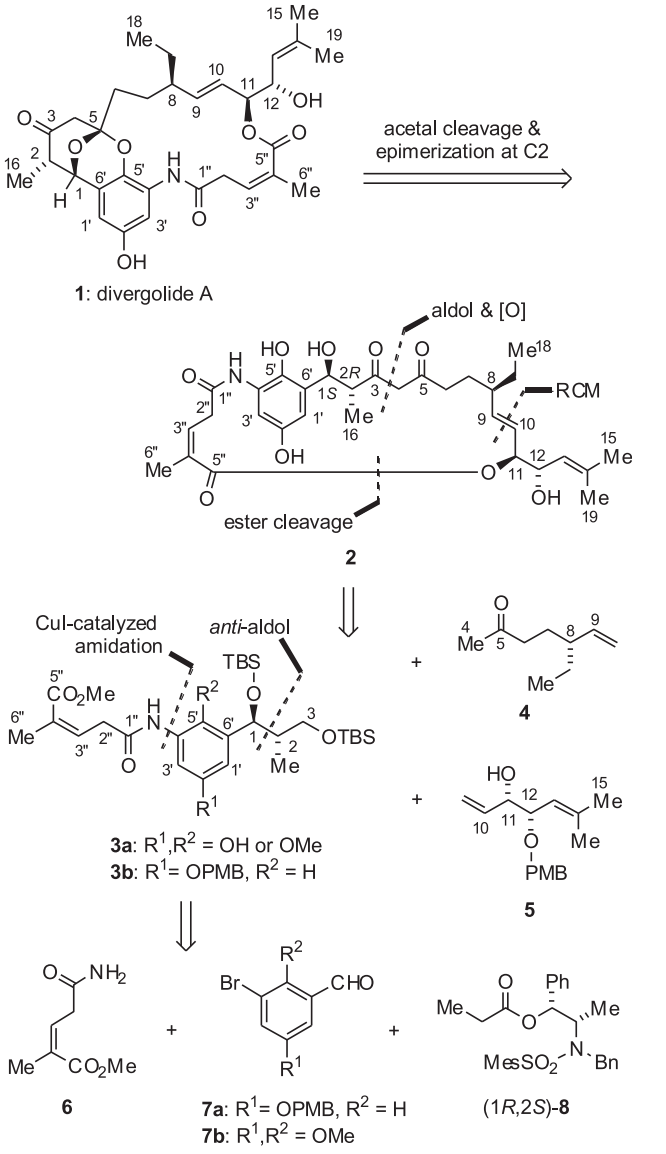
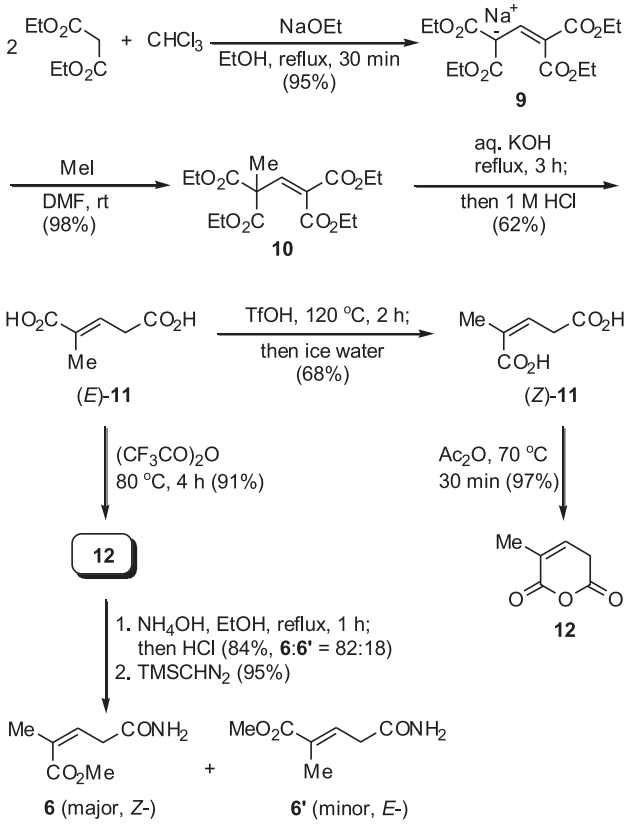


Fig. 1. The structure and retrosynthetic analysis of divergolide A (**1**).

epimerized during formation of the tricyclic acetal subunit. In this connection, we formulated our retrosynthetic analysis of **1** as shown in Fig. 1. The macrocyclic intermediate **2** could be derived by acetal cleavage and epimerization at C2 position of **1**. The (1*S*,2*R*)-configuration in **2** is the same as that of the proposed biosynthesis intermediates. Further bond disconnections were followed via the RCM reaction at the C9–C10 double bond, the ester bond cleavage, and the aldol–oxidation sequence at the C3–C4 single bond, leading to the ketone fragment **4**, the alcohol fragment **5**,[8] and the amido hydroquinone fragment **3a** (R^1,R^2=OH). The latter was sought to form from the precursor **3b** through a biomimetic redox process.[2,3,6,9] Finally, the compound **3b** could be assembled by the *anti*-selective aldol reaction of the chiral norephedrine-derived propionate **8**[10] and CuI-catalyzed amidation[11] of the amide **6** from the functionalized 3-bromobenzaldehyde **7a**, a synthetic equivalent to the ansamycin biosynthesis starter unit, 3-amino-5-hydroxybenzoic acid (AHBA). Alternatively, the same transformations starting from the 3-bromobenzaldehyde **7b** should give the protected amido hydroquinone fragment **3a** (R^1,R^2=OMe).

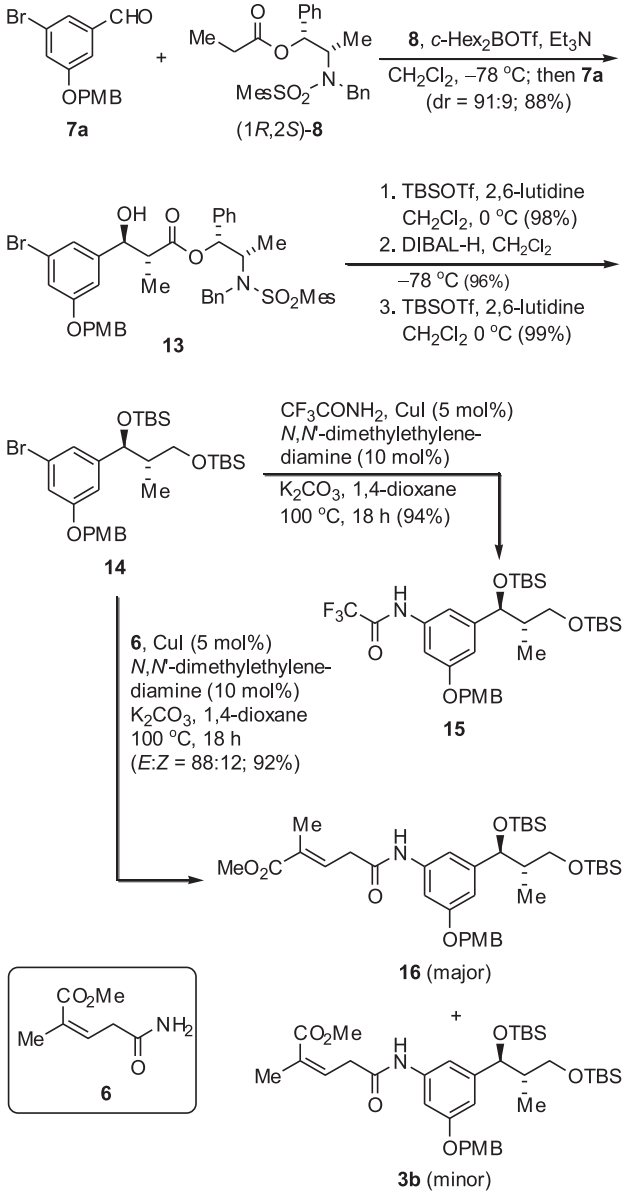
Our synthesis of methyl (*Z*)-4-carbamoyl-2-methylbut-2-enoate (**6**) is illustrated in Scheme 1. The known anhydride **12**[12] was prepared from (*Z*)- or (*E*)-γ-methylglutaconic acid [(*Z*)- or (*E*)-**11**][12,13] by a modified sequence. Reaction of diethyl malonate with $CHCl_3$ in the presence of NaOEt in refluxing EtOH gave sodio-1,1,3,3-tetracarboethoxypropene (**9**) as a yellow solid in 95% yield. Methylation of **9** with MeI at room temperature in DMF afforded 1,1,3,3-tetracarboethoxybutene (**10**) in 98% yield. Alkaline hydrolysis of **10** using aqueous KOH under reflux for 3 h furnished, after acidification with HCl, (*E*)-γ-methylglutaconic acid [(*E*)-2-methylpent-2-enedioic acid, (*E*)-**11**] in 62% yield. Kagan and co-workers examined isomerization of (*E*)-**11** into (*Z*)-**11** at 100 °C in FSO_3H and H_2SO_4, respectively, resulting in 46% yield of a mixture containing 2.5:1 ratio of (*Z*)-**11** and (*E*)-**11**.[12] Golding and co-workers treated (*E*)-**11** in refluxing triflic acid (TfOH, bp=162 °C) for 2 h to give, after quenching with ice water, a 9:1 mixture of (*Z*)-**11** and (*E*)-**11** in 46% combined yield.[13c] We repeated isomerization of (*E*)-**11** in triflic acid at 120 °C for 2 h, leading to an improved yield of 68% of (*Z*)-**11** in a similar (*Z*):(*E*) ratio of 9:1. Formation of (*Z*)-γ-methylglutaconic anhydride (**12**) from (*E*)-**11** was reported by Kagan and co-workers.[12] Thus, heating of a solution of (*E*)-**11** in CF_3CO_2H for 62 h at 100 °C resulted in a 1:1 mixture of (*E*)-**11** and **12** while treatment of a solution of (*E*)-**11** in refluxing Ac_2O (ca. 140 °C) for 2 h afforded **12**, after distillation, in ca. 30% yield.[12] We found that (*E*)-**11** could be transformed into **12** in 91% yield by heating in $(CF_3CO_2)O$ at 80 °C for 4 h. Alternatively, treatment of (*Z*)-**11** in Ac_2O at 70 °C for 30 min gave **12** in 97% yield. Finally, regioselective amide formation from **12** was performed by exposure to an ethanolic solution of NH_4OH[14] at reflux for 1 h to furnish an 84% yield of the corresponding (*Z*)-4-carbamoyl-2-methylbut-2-enoic acid as an 82:18 mixture of (*Z*)- and (*E*)-isomers. In the NMR spectra taken in DMSO-d_6, the major isomer shows the α-Me and β-H signals at 1.85 (d, *J*=1.2 Hz, 3H) and 6.11 (td, *J*=7.2, 1.6 Hz, 1H) ppm while those for the minor isomer appear at 1.73 (d, *J*=1.2 Hz, 3H) and 6.77 (td, *J*=7.2, 1.2 Hz, 1H) ppm. The ^{13}C NMR signals for the α-Me groups are found at 21.4 (major isomer) and 13.5 (minor isomer) ppm. These NMR data are



Scheme 1. Synthesis of γ-methylglutaconic anhydride **12** and the amide **6**.

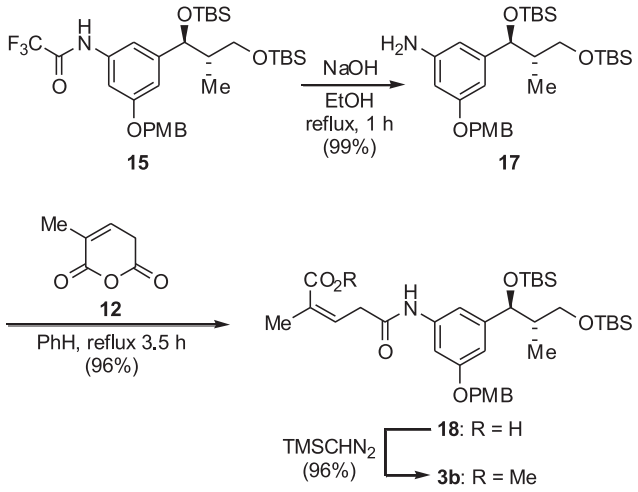
consistent with those observed for the known (*Z*)-**11** and (*E*)-**11**.[12,13c] Upon treatment with $TMSCHN_2$, the above crude acids were converted into the methyl esters in 95% yield and the minor (*E*)-isomer **6′** could be separated out by column chromatography over silica gel to give isomer pure **6**.

In our previous work,[6] we reported synthesis of the enantiomer (*en*-**14**) of the aryl bromide **14** using (1*S*,2*R*)-**8**[10] as the chiral propionate in the *anti*-selective aldol reaction with the 3-bromobenzaldehyde **7a**. As shown in Scheme 2, the same aldol reaction of (1*R*,2*S*)-**8** with **7a** afforded the *anti*-aldol product **13** in 88% yield and in a 91:9 diastereomeric ratio. Protection of the hydroxy group in **13** as the TBS ether (98% yield) and DIBAL-H reduction of the ester moiety gave the corresponding primary alcohol (96% yield). The latter was then converted into the bis-TBS ether **14** in 99% yield. We have reported the CuI-catalyzed amidation of *en*-**14** with acetamide and trifluoroacetamide, respectively, using *N*,*N*′-dimethylethylenediamine as the ligand to form the *N*-arylated amides in 91–94% yields.[6] In the same manner, the amidation of **14** with trifluoroacetamide produced **15** in 94% yield. Under the same amidation conditions, the reaction of the amide **6** with the aryl bromide **14** afforded the expected products in 92% combined yield and in an 88:12 ratio of **16** and **3b**. It is not surprising to note that the (*Z*)-configuration in **6** isomerized into the (*E*)-configuration under the basic conditions used for the CuI-catalyzed amidation. This observation further confirms the lability of the double bond configuration in (*Z*)-γ-methylglutaconic acid [(*Z*)-**11**] and its derivatives such as **3b** and **6** toward acidic and basic conditions.[12]



Scheme 2. Synthesis of the amido hydroquinone precursor **16**.

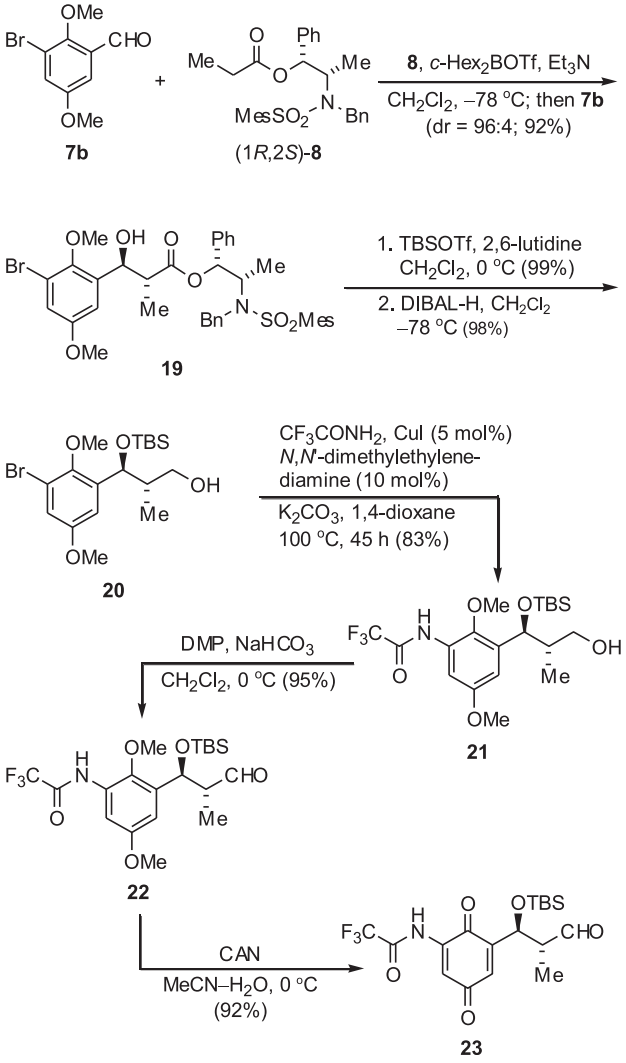
In order to suppress isomerization of the (*Z*)-double bond during the amidation process, we envisioned to use aminolysis of the anhydride **12** with the aniline derivative **17** in the absence of other basic species (Scheme 3).[15] Thus, alkaline hydrolysis of the *N*-aryl trifluoroacetamide **15** in refluxing EtOH in the presence of NaOH furnished the aniline **17** in 99% yield. Heating a mixture of **17** with the anhydride **12** in benzene at reflux for 3.5 h regioselectively gave the amide **18** with (*Z*)-configuration in 96% yield in an isomer pure form. Treatment of **18** with $TMSCHN_2$ gave the corresponding methyl ester **3b** in 96% yield. The configuration of the tri-substituted conjugated double bond in **3b** and **16** is assigned according to the α-Me and β-H signals in their NMR spectra taken in $CDCl_3$. The compound **3b** has the α-Me and β-H signals at 1.97 (s, 3H) and 6.27 (t, *J*=8.0 Hz, 1H) ppm while those for the compound **16** are found at 1.93 (s, 3H) and 7.00 (td, *J*=8.0, 0.5 Hz, 1H) ppm. The ^{13}C NMR signals of the α-Me group appear at 20.4 (for **3b**) and 12.9 (for **16**) ppm. By referencing to the NMR data of (*Z*)-**11**/(*E*)-**11**[12,13c] and (*Z*)-**6**/(*E*)-**6′**, the geometry of **3b** and **16** could be assigned.



Scheme 3. Synthesis of the amido hydroquinone precursor **3b**.

We demonstrated transformation of the acetamide analogue of **15** into the corresponding 1,4-benzoquinone by cleavage of the PMB ether and 2,6-DCPFC oxidation of the resultant 3-amidophenol.[6] Attempts at similar transformations from **15** and **18** met low yields (20–60%) of the desired 1,4-benzoquinones and poor reproducibility of the results. For facilitating the oxidation step, we synthesized the 1,4-dimethoxy-substituted analogue **21** as shown in Scheme 4. The *anti*-selective aldol reaction of **7b**[16] with (1*R*,2*S*)-**8** gave the aldol product **19** in 92% yield and in a 96:4 ratio of diastereomers. The *ortho*-OMe group in the aldehyde **7b** was found not interfering with asymmetric induction of the aldol reaction. After protection of the hydroxy group in **19** as the TBS ether (99% yield), the chiral auxiliary was removed by DIBAL-H reduction to afford the primary alcohol **20** in 98% yield. It was found that the free hydroxy group in **20** did not affect the subsequent amidation. Thus, the CuI-catalyzed amidation of **20** with CF_3CONH_2 at 100 °C for 45 h furnished the anilide **21** in 83% yield. Oxidation of **21** using DMP produced the aldehyde **22** (95% yield), which was subjected to

CAN oxidation[9a–c] at 0 °C for 15 min to furnish the 2-amido-1,4-benzoquinone **23** in 92% yield. These results demonstrated that oxidation of 1,4-dimethoxybenzenes to form the corresponding 1,4-benzoquinones is much more easy than phenols. Therefore, it could be considered as an alternative for total synthesis of divergolide A and its congeners.



Scheme 4. Synthesis and CAN oxidation of the 2,5-dimethoxyanilide **22**.

3. Conclusion

In summary, we have established an improved synthesis of γ-methylglutaconic anhydride (**12**)[12] and two methods for installation of (*E*)- and (*Z*)-γ-methylglutaconic acids onto a model 3-aminophenol core of divergolide A and E–H. Amidation of the aryl bromide **14** with methyl (*Z*)-4-carbamoyl-2-methylbut-2-enoate (**6**) under Cu(I) catalysis using *N*,*N*′-dimethylethylenediamine as the ligand and K_2CO_3 as the base gave the (*E*)-anilide **16** as the major product. On the other hand, aminolysis of the anhydride **12** with the aniline derivative **17** afforded exclusively the (*Z*)-anilide **3b**. Moreover, the 1,4-dimethoxy-substituted anilide **22** has been synthesized and transformed into the 1,4-benzoquinone **23** in excellent yield upon CAN oxidation. Our results on these model studies reveal the lability of the (*Z*)-configuration in γ-methylglutaconic acid and its derivatives toward both acidic and basic conditions, which should be of reference value for total synthesis of divergolide A and E–H.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 (400 or 500 MHz for ^{1}H and 100 or 125 MHz for ^{13}C, respectively). Residual solvent peaks are used as the internal reference; the signals at 7.26 and 77.00 ppm are set for ^{1}H and ^{13}C NMR spectra, respectively, taken in $CDCl_3$ while the signals at 2.50 and 40.45 ppm are set for ^{1}H and ^{13}C NMR spectra, respectively, taken in DMSO-d_6. IR spectra were taken on an FTIR spectrophotometer. High resolution mass spectra (HRMS) were measured by TOF MS under the +EI conditions. Silica gel plates pre-coated on glass were used for thin-layer chromatography using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. Silica gel was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Petroleum ether (PE) of bp 60–90 °C was used. Reagents were obtained commercially and used as received.

4.2. Sodio-1,1,3,3-tetracarboethoxypropene (9)[12,13c]

To a solution of NaOEt (9.20 g, 135.00 mmol) in dry EtOH (80 mL) were added dropwise diethyl malonate (12.10 g, 11.5 mL, 76.00 mmol) and chloroform (3.05 mL, 38.00 mmol). The resultant mixture was heated at reflux for 30 min. The hot yellow-colored reaction mixture was filtered off with washing by warm EtOH. The combined filtrate was cooled to room temperature and evaporated under reduced pressure. The residue was recrystallized from EtOH (60 mL) at 0 °C to give **9** (12.80 g, 95%) as a yellow solid. Mp 268–270 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (s, 1H), 3.94 (q, J=7.2 Hz, 8H), 1.15 (t, J=7.2 Hz, 12H).

4.3. 1,1,3,3-Tetracarboethoxybutene (10)[12,13c]

To a solution of **9** (12.80 g, 36.00 mmol) in dry DMF (25 mL) was added MeI (25.80 g, 11.5 mL, 180.00 mmol) dropwise over 15 min. The resultant mixture was stirred at room temperature overnight. The reaction mixture was diluted with water (100 mL) and extracted with Et_2O (150 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give **10** (12.10 g, 98%) as a pale yellow oil. R_f=0.34 (2.4% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 4.26–4.16 (m, 8H), 1.64 (s, 3H), 1.32–1.22 (m, 12H).

4.4. (*E*)-γ-Methylglutaconic acid [(*E*)-11][12,13c]

To an aqueous solution of KOH (2.5 M, 120 mL) was added neat **10** (12.10 g, 35.00 mmol) dropwise followed by heating at reflux for 3 h. The reaction mixture was cooled to room temperature and acidified with 1 M aqueous HCl solution to pH 3. The resultant mixture was extracted with EtOAc (200 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was recrystallized in MeCN (30 mL) at −10 °C to give (*E*)-**11** (3.10 g, 62%) as a white solid. Mp 139–141 °C (MeCN); IR (film): 3000–2800 (br), 1678, 1274, 1223 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.39 (br s, 2H), 6.78–6.75 (m, 1H), 3.20 (dd, J=7.2, 1.2 Hz, 2H), 1.72 (d, J=1.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.8, 169.5, 134.9, 130.7, 34.7, 13.5; HRMS (+EI) calcd for $C_6H_8O_4$ 144.0423 (M^+), found 144.0425.

4.5. (*Z*)-γ-Methylglutaconic acid [(*Z*)-11][12,13c]

A solution of (*E*)-**11** (300.0 mg, 2.10 mmol) in triflic acid (2 mL) was heated at 120 °C for 2 h. The hot deep brown oil was quenched with ice water. The mixture was cooled to room temperature and

extracted with EtOAc (5 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give a 9:1 mixture of (*Z*)-**11** and (*E*)-**11** (204.0 mg, 68%) as a yellow solid. Mp 119–121 °C (MeCN); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.4 (br s, 2H), 6.11 (td, *J*=7.2, 1.6 Hz, 1H), 3.45 (dd, *J*=7.2, 1.2 Hz, 2H), 1.85 (d, *J*=1.2 Hz, 3H).

4.6. γ-Methylglutaconic anhydride (12)[12]

4.6.1. Method A. A 10-mL pressurized process vial was charged with (*E*)-**11** (212.4 mg, 1.47 mmol) and 2,2,2-trifluoroacetic anhydride (1 mL). The vial was sealed with a cap containing a silicon septum. The vial was heated in an oil bath at 80 °C for 4 h. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, CH_2Cl_2) to give **12** (168.7 mg, 91%) as a pale yellow solid. Mp 74–75 °C (CH_2Cl_2); R_f=0.42 (25% EtOAc in PE); IR (film): 1801, 1743, 1270, 1041 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64–6.61 (m, 1H), 3.54–3.52 (m, 2H), 2.04–2.02 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 161.1, 136.9, 126.6, 32.3, 16.6; HRMS (+EI) calcd for $C_6H_6O_3$ 126.0317 (M^+), found 126.0315.

4.6.2. Method B. A solution of (*Z*)-**11** (138.3 mg, 0.96 mmol) in acetic anhydride (3 mL) was heated at 70 °C for 30 min. The dark brown reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, CH_2Cl_2) to give **12** (117.3 mg, 97%) as a pale yellow solid.

4.7. Methyl (*Z*)-4-carbamoyl-2-methylbut-2-enoate (6)

A mixture of **12** (208.2 mg, 1.65 mmol) and concentrated aqueous NH_4OH (4 mL) in EtOH (95%, 7 mL) was heated at reflux for 4 h. The reaction mixture was cooled to −10 °C and acidified with diluted aqueous HCl to pH 4. The resultant mixture was extracted with EtOAc (10 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 50% EtOAc in PE) to give an 82:18 mixture of (*Z*)-4-carbamoyl-2-methylbut-2-enoic acid (198.5 mg, 84%) as a pale yellow solid. Mp 98–100 °C (MeOH); R_f=0.38 (50% EOAc in PE); IR (film): 3418 (br), 1662, 1000 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.4 (br s, 3H), 6.77 (td, *J*=7.2, 1.6 Hz, 0.18H) [for (*E*)-isomer], 6.11 (td, *J*=7.2, 1.6 Hz, 0.82H) [for (*Z*)-isomer], 3.45 (dd, *J*=7.2, 1.2 Hz, 1.64H) [for (*Z*)-isomer], 3.20 (dd, *J*=7.2, 1.2 Hz, 0.36H) [for (*E*)-isomer], 1.85 (d, *J*=1.2 Hz, 2.46H) [for (*Z*)-isomer], 1.73 (d, *J*=1.2 Hz, 0.54H) [for (*E*)-isomer]; ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 169.5, 134.8 [for (*E*)-isomer], 134.5, 130.3, 35.3, 34.6 [for (*E*)-isomer], 21.4, 13.5 [for (*E*)-isomer]; HRMS (+EI) calcd for $C_6H_9NO_3$ 143.0582 (M^+), found 143.0583.

To a solution of the above monoacid (54.4 mg, 0.38 mmol) in benzene (4 mL) and MeOH (1 mL) was added a solution of $TMSCHN_2$ (0.38 mL, 2.0 M in hexane, 0.76 mmol) dropwise. The resultant yellow solution was allowed to stir at room temperature for 2 h. The reaction mixture was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, 10% EtOAc–PE) to give **6** (56.7 mg, 95%) as a pale yellow oil. R_f=0.44 (10% EtOAc in PE); IR (film): 3428, 3348, 3201, 1704, 1664, 1228, 1134 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (br s, 1H, $CONH_2$), 6.24–6.20 (m, 1H), 5.77 (br s, 1H, $CONH_2$), 3.74 (s, 3H), 3.40 (dd, *J*=7.6, 0.8 Hz, 2H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 168.3, 135.3, 130.0, 51.7, 37.0, 20.3; HRMS (+EI) calcd for $C_7H_{11}NO_3$ 157.0739 (M^+), found 157.0738.

4.8. 3-Bromo-5-((*p*-methoxybenzyl)oxy)benzaldehyde (7a)

To a solution of 1,3-dibromo-5-((4-methoxybenzyl)oxy)-benzene[17] (440.3 mg, 1.20 mmol) in anhydrous THF (15 mL) cooled at −95 °C under N_2 was added *n*-BuLi (0.8 mL, 1.30 mmol, 1.6 M in hexanes) dropwise in 5 min followed by stirring at same temperature for 1 h. To the resultant mixture was added anhydrous DMF (0.9 mL, 12.00 mmol). The reaction mixture was allowed to warm to room temperature, quenched with saturated aqueous NH_4Cl, and extracted with EtOAc (15 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 4.8% EtOAc in PE) to give the aldehyde **7a** (321.2 mg, 85%) as a colorless oil. R_f=0.40 (4.8% EtOAc in PE); IR (film): 1699, 1244, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (d, *J*=2.0 Hz, 1H), 7.56 (br s, 1H), 7.38–7.32 (m, 4H), 6.95–6.90 (m, 2H), 5.02 (s, 2H), 3.81 (d, *J*=0.8 Hz 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 159.9, 159.6, 138.6, 129.3 (×2), 127.6, 125.7, 124.5, 123.4, 114.0 (×2), 113.0, 70.3, 55.2; HRMS (+EI) calcd for $C_{15}H_{13}BrO_3$ 320.0048 (M^+), found 320.0047.

4.9. (1*R*,2*S*)-2-{*N*-Benzyl-*N*-[(2′,4′,6′-trimethylbenzene)-sulfonyl]amino}-1-phenylpropyl (2*R*,3*S*)-3-{3′-bromo-5′-[(4″-methoxybenzyl)oxy]phenyl}-3-hydroxy-2-methylpropionate (13)

To a solution of the chiral propionate (1*R*,2*S*)-**8** (950.3 mg, 2.00 mmol) in anhydrous CH_2Cl_2 (150 mL) cooled at −78 °C was added Et_3N (0.70 mL, 5.00 mmol) under a nitrogen atmosphere. After stirring at the same temperature for 5 min, a solution of *c*-Hex_2BOTf (1.0 M in hexane, 6.00 mL, 6.00 mmol) was added dropwise over 20 min. The resultant mixture was stirred at the same temperature for 2 h. A solution of the aldehyde **7a** (803.2 mg, 2.50 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise followed by stirring at the same temperature for 1 h. The mixture was allowed to warm to −50 °C over 1 h and the reaction was quenched by addition of a mixture of pH 7 buffer and MeOH (1/1, v/v, 20 mL). The reaction mixture was diluted with MeOH to make a homogeneous solution. After careful addition of 30% H_2O_2 (8 mL), the mixture was stirred at room temperature for 6 h and then evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 (100 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 14.3% EtOAc in PE) to give the *anti*-aldol product **13** (1.400 g, 88%, dr=91:9) as a colorless viscous oil. R_f=0.32 (14.3% EtOAc in PE); $[\alpha]_D^{20}$ −8.3 (*c* 0.32, $CHCl_3$); IR (film): 3408 (br), 1727, 1600, 1493, 1314, 1149 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.16 (m, 10H), 7.09 (br s, 1H), 7.04 (t, *J*=2.0 Hz, 1H), 6.93–6.89 (m, 2H), 6.89 (s, 2H), 6.86 (dd, *J*=2.0, 1.6 Hz, 1H) 6.84 (d, *J*=1.6 Hz, 1H), 6.82 (d, *J*=2.0 Hz, 1H), 5.83 (d, *J*=4.0 Hz, 1H), 4.93 (s, 2H), 4.71 and 4.49 (ABq, *J*=16.8 Hz, 2H), 4.61 (dd, *J*=8.0, 4.8 Hz, 1H), 4.10–4.04 (m, 1H), 3.82 (s, 3H), 3.16 (d, *J*=4.8 Hz, 1H, OH), 2.72–2.65 (m, 1H), 2.50 (s, 6H), 2.29 (s, 3H), 1.12 (d, *J*=6.8 Hz, 3H), 0.97 (d, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 159.6, 159.6, 144.8, 142.6, 140.3 (×2), 138.6, 138.1, 133.4, 132.1 (×2), 129.3 (×2), 128.5 (×2), 128.4 (×2), 128.1, 128.0, 127.6 (×2), 127.2, 125.7 (×2), 122.9, 122.1, 117.4, 114.0 (×2), 112.6, 78.6, 75.6, 70.1, 56.8, 55.3, 48.2, 46.9, 22.9 (×2), 20.9, 14.5, 13.1; HRMS (+EI) calcd for $C_{43}H_{46}BrNO_7S$ 799.2178 (M^+), found 799.2175.

4.10. (1*R*,2*S*)-2-{*N*-Benzyl-*N*-[(2′,4′,6′-trimethylbenzene)-sulfonyl]amino}-1-phenylpropyl (2*R*,3*S*)-3-{3′-bromo-5′-[(4″-methoxybenzyl)oxy]phenyl}-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropionate

To a solution of the alcohol **13** (880.8 mg, 1.10 mmol) in anhydrous CH_2Cl_2 (10 mL) cooled at 0 °C was sequentially added 2,6-lutidine (0.25 mL, 2.20 mmol) and TBSOTf (0.4 mL, 1.60 mmol) under a nitrogen atmosphere. After stirring at 0 °C for 1 h, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ at

0 °C. The reaction mixture was then extracted with CH_2Cl_2 (15 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 9.1% EtOAc in PE) to give the corresponding TBS ether (911.6 mg, 98%) as a colorless viscous oil. R_f=0.35 (9.1% EtOAc in PE); $[\alpha]_D^{20}$ −21.4 (*c* 0.40, $CHCl_3$); IR (film): 2938, 1741, 1602, 1450, 1319, 1249, 1154, 103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J*=7.2 Hz, 2H), 7.33–7.23 (m, 5H), 7.16 (t, *J*=7.2 Hz, 1H), 7.08 (t, *J*=7.2 Hz, 2H), 7.01 (s, 2H), 6.93–6.87 (m, 2H), 6.88 (s, 2H), 6.73 (t, *J*=1.6 Hz, 1H), 6.70 (s, 1H), 6.68 (s, 1H), 5.73 (d, *J*=5.6 Hz, 1H), 4.89 and 4.82 (ABq, *J*=11.2 Hz, 2H), 4.86 and 4.46 (ABq, *J*=16.4 Hz, 2H), 4.67 (d, *J*=8.8 Hz, 1H), 4.04–4.01 (m, 1H), 3.81 (s, 3H), 2.68–2.61 (m, 1H), 2.44 (s, 6H), 2.31 (s, 3H), 1.15 (d, *J*=7.2 Hz, 3H), 0.79 (s, 9H), 0.72 (d, *J*=7.2 Hz, 3H), −0.05 (s, 3H), −0.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 159.5, 159.2, 145.3, 142.4, 140.4 (×2), 138.6, 138.1, 133.0, 132.1 (×2), 129.2 (×2), 128.4 (×2), 128.2 (×2), 128.2, 128.2 (×2), 127.8, 127.4, 126.2 (×2), 122.6, 122.5, 117.4, 114.0 (×2), 112.8, 77.9, 76.1, 70.0, 56.7, 55.3, 48.6, 48.2, 25.8 (×3), 22.9 (×2), 20.9, 18.1, 14.3, 13.4, −4.7, −5.0; HRMS (+EI) calcd for $C_{49}H_{60}BrNO_7SSi$ 913.3043 (M^+), found 913.3049.

4.11. (2*S*,3*S*)-3-{3′-Bromo-5′-[(4″-methoxybenzyl)oxy]-phenyl}-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropan-1-ol

To a solution of the above TBS ether (1.522 g, 1.80 mmol) in anhydrous CH_2Cl_2 (20 mL) cooled at −78 °C was added DIBAL-H (1.0 M in hexane, 3.60 mL, 3.60 mmol) followed by stirring at the same temperature for 45 min. The reaction was quenched by careful addition of MeOH (5 mL) at −78 °C and the reaction mixture was allowed to warm to room temperature. A saturated aqueous solution of sodium potassium tartrate (20 mL) was added and the resultant mixture was stirred at room temperature for about 1 h. The mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 7.7% EtOAc in PE) to give the primary alcohol (856.2 mg, 96%) as a colorless oil. R_f=0.30 (7.7% EtOAc in PE); $[\alpha]_D^{20}$ −12.2 (*c* 0.47, $CHCl_3$); IR (film): 3448 (br), 2933, 1601, 1575, 1515, 1446, 1249, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.32 (m, 2H), 7.03 (br s, 2H), 6.93–6.90 (m, 2H), 6.84 (br s, 1H), 4.98 and 4.94 (ABq, *J*=11.2 Hz, 2H), 4.49 (d, *J*=6.8 Hz, 1H), 3.82 (s, 3H), 3.66–3.53 (m, 2H), 2.65 (br s, 1H, OH), 1.90–1.84 (m, 1H), 0.89 (s, 9H), 0.85 (d, *J*=6.8 Hz, 3H), 0.05 (s, 3H), −0.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 159.3, 146.9, 129.3 (×2), 128.3, 122.4, 122.3, 117.0, 114.0 (×2), 112.2, 79.7, 70.1, 65.8, 55.3, 43.0, 25.8 (×3), 18.1, 14.2, −4.5, −5.2; HRMS (+EI) calcd for $C_{24}H_{35}BrO_4Si$ 494.1488 (M^+), found 494.1485.

4.12. (1′*S*,2′*S*)-1-Bromo-3-{1′,3′-bis[(*tert*-butyldimethylsilyl)-oxy]-2′-methylporpyl}-5-[(4″-methoxybenzyl)oxy]benzene (14)

To a solution of the above primary alcohol (743.3 mg, 1.50 mmol) in anhydrous CH_2Cl_2 (15 mL) cooled at 0 °C was sequentially added 2,6-lutidine (0.34 mL, 3.00 mmol) and TBSOTf (0.55 mL, 2.20 mmol) under a nitrogen atmosphere followed by stirring at same temperature for 1 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ at 0 °C and the reaction mixture was extracted with CH_2Cl_2 (15 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 1.2% EtOAc in PE) to give **14** (905.6 mg, 99%) as a colorless oil. R_f=0.30 (1.2% EtOAc in PE); $[\alpha]_D^{20}$ −39.2 (*c* 0.84, $CHCl_3$); IR (film): 2933, 1601, 1576, 1515, 1462, 1250, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.32 (m, 2H), 7.02 (s, 1H), 6.99 (t, *J*=2.0 Hz, 1H), 6.92–6.89 (m, 2H), 6.84 (s, 1H), 4.96 and 4.93 (ABq, *J*=10.8 Hz, 2H), 4.56 (d, *J*=7.2 Hz, 1H), 3.82 (s, 3H), 3.57 and 3.47 (ABqd, *J*=10.0, 5.6 Hz, 2H), 1.91–1.84 (m, 1H), 1.56 (s, 3H), 0.91 (s, 9H), 0.85 (s, 9H), 0.65 (d, *J*=6.8 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H), −0.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 159.1, 146.8, 129.2 (×2), 128.5, 122.7, 122.0, 116.7, 114.0 (×2), 112.6, 75.1, 70.0, 64.4, 55.3, 43.8, 26.0 (×3), 25.8 (×3), 18.3, 18.1, 12.5, −4.6, −5.1, −5.3, −5.4; HRMS (+EI) calcd for $C_{30}H_{49}BrO_4Si_2$ 608.2353 (M^+), found 608.2359.

4.13. *N*-(1′*S*,2′*S*)-3-{1′,3′-Bis[(*tert*-butyldimethylsilyl)oxy]-2′-methylporpyl}-5-[(4″-methoxybenzyl)oxy]phenyl 2,2,2-trifluoroacetamide (15)

An over-dried Schlenk tube was charged with CuI (10.0 mg, 5.0×10^{-2} mmol), K_2CO_3 (276.4 mg, 2.00 mmol) and 4 Å MS (500 mg). The tube was evacuated and backfilled with nitrogen several times. Then, a solution of the aryl bromide **14** (609.9 mg, 1.00 mmol), 2,2,2-trifluoroacetamide (170.2 mg, 1.50 mmol), and *N*,*N*′-dimethylethylenediamine (12 μL, 0.10 mmol) in degassed anhydrous 1,4-dioxane (3.0 mL) was added under nitrogen through a syringe. The tube was heated at 100 °C for 18 h. The reaction mixture was cooled to room temperature and extracted with EtOAc (7 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 4.8% EtOAc in PE) to give **15** (603.5 mg, 94%) as a pale yellow oil. R_f=0.36 (4.8% EtOAc in PE); $[\alpha]_D^{20}$ −30.0 (*c* 0.52, $CHCl_3$); IR (film): 3306 (br), 2936, 1715, 1611, 1462, 1249, 1170, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (br s, 1H, NH), 7.37–7.34 (m, 2H), 7.33 (t, *J*=2.0 Hz, 1H), 6.93–6.90 (m, 2H), 6.91 (s, 1H), 6.81 (s, 1H), 5.01 and 4.97 (ABq, *J*=11.2 Hz, 2H), 4.57 (d, *J*=6.8 Hz, 1H), 3.82 (s, 3H), 3.60 and 3.52 (ABqd, *J*=10.0, 6.0 Hz, 2H), 1.91–1.84 (m, 1H), 0.92 (s, 9H), 0.87 (s, 9H), 0.66 (d, *J*=6.8 Hz, 3H), 0.05 (s, 6H), 0.02 (s, 3H), −0.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 159.1, 154.4 ($^2J_{C,F}$=37.2 Hz), 146.4, 135.5, 129.2 (×2), 128.6, 115.7 ($^1J_{C,F}$=288.9 Hz), 114.0 (×2), 111.7, 111.3, 105.8, 75.4, 69.9, 64.4, 55.3, 43.9, 25.9 (×3), 25.8 (×3), 18.3, 18.1, 12.7, −4.6, −5.2, −5.3, −5.5; HRMS (+EI) calcd for $C_{32}H_{50}F_3NO_5Si_2$ 641.3180 (M^+), found 641.3185.

4.14. Methyl (2*E*,1″*S*,2″*S*)-4-{3′-[1″,3″-bis((*tert*-butyldi-methylsilyl)oxy)-2″-methylporpyl]-5′-[(4‴-methoxybenzyl)-oxy]phenylcarbomoyl}-2-methylbut-2-enoate (16) and methyl (2*Z*,1″*S*,2″*S*)-4-{3′-[1″,3″-bis((*tert*-butyldimethylsilyl)oxy)-2″-methylporpyl]-5′-[(4‴-methoxybenzyl)oxy]-phenyl-carbomoyl}-2-methylbut-2-enoate (3b)

An over-dried Schlenk tube was charged with CuI (3.0 mg, 1.5×10^{-2} mmol), K_2CO_3 (82.9 mg, 0.60 mmol) and 4 Å MS (150 mg). The tube was evacuated and backfilled with nitrogen several times. Then, a solution of the aryl bromide **14** (183.0 mg, 0.30 mmol), **6** (70.8 mg, 0.45 mmol), and *N*,*N*′-dimethylethylenediamine (3.6 μL, 3.0×10^{-2} mmol) in degassed anhydrous 1,4-dioxane (1.0 mL) was added under nitrogen through a syringe. The tube was heated at 100 °C for 18 h. The reaction mixture was cooled to room temperature and extracted with EtOAc (5 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 6.3% EtOAc in PE) to give an 88:12 mixture of **16** and **3b** (189.4 mg, 92% combined yield). Compound **16**: a pale yellow oil; R_f=0.48 (6.3% EtOAc in PE); $[\alpha]_D^{20}$ −27.5 (*c* 0.36, $CHCl_3$); IR (film): 3337, 2933, 1705, 1605, 1463, 1249, 1078 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.34 (m, 3H), 7.12 (s, 1H), 7.00 (td, *J*=8.0, 0.5 Hz, 1H), 6.90–6.89 (m, 2H), 6.78 (s, 1H), 6.70 (s, 1H), 4.99 and 4.96 (ABq, *J*=11.0 Hz, 2H), 4.50 (d, *J*=7.0 Hz, 1H),

3.81 (s, 3H), 3.77 (s, 3H), 3.58 (ABqd, J=10.0, 6.5 Hz, 1H), 3.55 (ABqd, J=10.0, 5.5 Hz, 1H), 3.30 (d, J=7.0 Hz, 2H), 1.923 (s, 3H), 1.89–1.83 (m, 1H), 0.91 (s, 9H), 0.86 (s, 9H), 0.66 (d, J=7.0 Hz, 3H), 0.04 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H), −0.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 167.1, 159.4, 159.0, 145.9, 138.0, 132.9, 131.8, 129.2 (×2), 129.0, 113.9 (×2), 110.7, 110.2, 105.2, 75.7, 69.8, 64.6, 55.3, 52.0, 43.9, 37.4, 26.0 (×3), 25.8 (×3), 18.3, 18.1, 12.9, 12.9, −4.6, −5.1, −5.3, −5.4; HRMS (+EI) calcd for $C_{37}H_{59}NO_7Si_2$ 685.3830 (M^+), found 685.3833. Compound **3b**: a pale yellow oil; R_f=0.46 (6.3% EtOAc in PE); $[\alpha]_D^{20}$ −18.1 (*c* 0.27, $CHCl_3$); IR (film): 3312, 2950, 2858, 1710, 1609, 1463, 1437, 1248, 1080 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H, NH), 7.37 (s, 1H), 7.37–7.34 (m, 2H), 6.91–6.89 (m, 2H), 6.81 (s, 1H), 6.65 (s, 1H), 6.27 (t, J=8.0 Hz, 1H), 4.99 and 4.95 (ABq, J=11.2 Hz, 2H), 4.50 (d, J=7.2 Hz, 1H), 3.81 (s, 3H), 3.81 (s, 3H), 3.57 (d, J=5.6 Hz, 2H), 3.52–3.40 (m, 2H), 1.97 (s, 3H), 1.90–1.83 (m, 1H), 0.90 (s, 9H), 0.86 (s, 9H), 0.68 (d, J=6.8 Hz, 3H), 0.03 (s, 6H), 0.00 (s, 3H), −0.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 168.2, 159.3, 158.8, 145.7, 138.8, 135.4, 130.4, 129.2 (×2), 129.1, 113.9 (×2), 110.5, 109.4, 104.8, 75.7, 69.7, 64.6, 55.3, 52.0, 43.9, 39.5, 26.0 (×3), 25.8 (×3), 20.4, 18.3, 18.1, 13.0, −4.6, −5.2, −5.3, −5.4; HRMS (+EI) calcd for $C_{37}H_{59}NO_7Si_2$ 685.3830 (M^+), found 685.3833.

4.15. (1′*S*,2′*S*)-3-{1′,3′-Bis[(*tert*-butyldimethylsilyl)oxy]-2′-methylporpyl}-5-[(4″-methoxybenzyl)oxy]aniline (17)

To a solution of **15** (141.2 mg, 0.22 mmol) in EtOH (95%, 4 mL) was added solid NaOH (40.0 mg, 1.00 mmol) followed by heating at reflux for 1 h. After cooling to room temperature, the reaction mixture was diluted by H_2O (20 mL) and extracted with EtOAc (15 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 11.1% EtOAc in PE) to give **17** (118.9 mg, 99%) as a colorless oil. R_f=0.42 (11.1% EtOAc in PE); $[\alpha]_D^{20}$ −33.2 (*c* 0.47, $CHCl_3$); IR (film): 3471, 3377, 2954, 2931, 2857, 1600, 1515, 1466, 1250, 1170, 1076, 1035 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.32 (m, 2H), 6.92–6.88 (m, 2H), 6.35 (s, 1H), 6.24 (s, 1H), 6.20 (t, J=2.0 Hz, 1H), 4.94 and 4.91 (ABq, J=11.2 Hz, 2H), 4.42 (d, J=7.2 Hz, 1H), 3.81 (s, 3H), 3.60 (ABqd, J=9.6, 5.2 Hz, 1H), 3.56 (ABqd, J=9.6, 6.0 Hz, 1H), 1.90–1.81 (m, 1H), 0.91 (s, 9H), 0.86 (s, 9H), 0.68 (d, J=6.8 Hz, 3H), 0.04 (s, 6H), 0.00 (s, 3H), −0.19 (s, 3H) (The two proton signals for NH_2 are not observed.); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 159.3, 146.6, 146.2, 129.3, 129.2 (×2), 113.9 (×2), 107.2, 104.2, 101.0, 76.0, 69.6, 64.7, 55.3, 43.9, 26.0 (×3), 25.9 (×3), 18.3, 18.2, 13.1, −4.6, −5.1, −5.3, −5.4; HRMS (+EI) calcd for $C_{30}H_{51}NO_4Si_2$ 545.3357 (M^+), found 545.3361.

4.16. (2*Z*,1″*S*,2″*S*)-4-{3′-[1″,3″-Bis((*tert*-butyldimethyl-silyl)-oxy)-2″-methylporpyl]-5′-[(4‴-methoxybenzyl)oxy]-phenyl-carbomoyl}-2-methylbut-2-enoic acid (18)

A solution of **12** (25.3 mg, 0.20 mmol) and **17** (81.9 mg, 0.15 mmol) in PhH (5 mL) was heated at reflux for 3.5 h. The reaction mixture was cooled to room temperature and extracted with EtOAc (5 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 28.6% EtOAc in PE) to give **18** (96.8 mg, 96%) as a pale yellow oil. R_f=0.30 (28.6% EtOAc in PE); $[\alpha]_D^{20}$ −18.3 (*c* 0.39, $CHCl_3$); IR (film): 3299, 2932, 2891, 2857, 1691, 1609, 1463, 1248, 1078, 1037 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (br s, 1H, NH), 7.37–7.33 (m, 2H), 7.32 (s, 1H), 6.91–6.89 (m, 2H), 6.83 (s, 1H), 6.68 (s, 1H), 6.37 (t, J=7.0 Hz, 1H), 4.98 and 4.95 (ABq, J=11.5 Hz, 2H), 4.49 (d, J=7.0 Hz, 1H), 3.81 (s, 3H), 3.57 (d, J=5.5 Hz, 2H), 3.60–3.50 (m, 2H), 2.02 (s, 3H), 1.90–1.82 (m, 1H), 0.90 (s, 9H), 0.85 (s, 9H), 0.67 (d, J=7.0 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H), −0.22 (s, 3H) (The proton signal for CO_2H is not observed.); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 168.6, 159.3, 158.9, 145.9, 138.4, 136.2, 130.5, 129.3 (×2), 128.9, 113.9 (×2), 110.7, 109.8, 105.1, 75.8, 69.8, 64.6, 55.3, 43.9, 39.0, 26.0 (×3), 25.7 (×3), 20.4, 18.3, 18.1, 13.0, −4.6, −5.2, −5.3, −5.4; HRMS (+EI) calcd for $C_{36}H_{57}NO_7Si_2$ 671.3674 (M^+), found 671.3676.

4.17. Formation of methyl ester 3b from 18

To a solution of **18** (10.1 mg, 1.5×10^{-2} mmol) PhH (1 mL) and MeOH (0.3 mL) was added $TMSCHN_2$ (15 μL, 2.0 M in hexane, 3.0×10^{-2} mmol) dropwise. The resultant yellow solution was allowed to stir at room temperature for 2 h. The reaction mixture was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, 6.3% EtOAc in PE) to give **3b** (9.9 mg, 96%) as a pale yellow oil.

4.18. (1*R*,2*S*)-2-{*N*-Benzyl-*N*-[(2′,4′,6′-trimethylbenzene)-sulfonyl]amino}-1-phenylpropyl (2*R*,3*S*)-3-(3′-bromo-2′,5′-dimethoxyphenyl)-3-hydroxy-2-methylpropionate (19)

To a solution of the chiral propionate (1*R*,2*S*)-**8** (950.3 mg, 2.00 mmol) in anhydrous CH_2Cl_2 (150 mL) cooled at −78 °C was added Et_3N (0.70 mL, 5.00 mmol) under a nitrogen atmosphere. After stirring at the same temperature for 5 min, a solution of *c*-Hex_2BOTf (1.0 M in hexane, 6.00 mL, 6.00 mmol) was added dropwise over 20 min. The resultant mixture was stirred at the same temperature for 2 h. A solution of the aldehyde **7b** (612.7 mg, 2.50 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise followed by stirring at the same temperature for 1 h. The mixture was allowed to warm to −50 °C over 1 h and the reaction was quenched by addition of a mixture of pH 7 buffer and MeOH (1/1, v/v, 20 mL). The reaction mixture was diluted with MeOH to make a homogeneous solution. After careful addition of 30% H_2O_2 (8 mL), the mixture was stirred at room temperature for 6 h and then evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 (100 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 11.1% EtOAc in PE) to give the *anti*-aldol product **19** (1.333 g, 92%, dr=96:4) as a colorless viscous oil. R_f=0.16 (9.1% EtOAc in PE); $[\alpha]_D^{20}$ −9.5 (*c* 0.78, $CHCl_3$); IR (film): 3502 (br), 2984, 2939, 1738, 1602, 1467, 1317, 1151, 1046, 1001 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.12 (m, 8H), 6.98 (d, J=3.2 Hz, 1H), 6.85 (s, 2H), 6.78 (d, J=7.2 Hz, 2H), 6.73 (d, J=2.8 Hz, 1H), 5.87 (d, J=3.6 Hz, 1H), 5.02 (t, J=6.8 Hz, 1H), 4.72 and 4.46 (ABq, J=16.4 Hz, 2H), 4.15–4.08 (m, 1H), 3.80 (s, 3H), 3.61 (s, 3H), 3.52 (d, J=6.0, 1H, OH), 2.97–2.89 (m, 1H), 2.49 (s, 6H), 2.27 (s, 3H), 1.17 (d, J=6.8 Hz, 3H), 1.11 (d, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 156.3, 148.0, 142.6, 140.2 (×2), 138.0, 137.9, 136.8, 133.3, 132.1 (×2), 128.3 (×2), 128.3 (×2), 127.8, 127.5 (×2), 127.1, 125.7 (×2), 118.4, 117.2, 111.6, 78.7, 71.1, 61.5, 57.0, 55.6, 48.4, 46.4, 22.9 (×2), 20.9, 14.5, 13.4; HRMS (+EI) calcd for $C_{37}H_{42}BrNO_7S$ 723.1865 (M^+), found 723.1874.

4.19. (1*R*,2*S*)-2-{*N*-Benzyl-*N*-[(2′,4′,6′-trimethylbenzene)-sulfonyl]amino}-1-phenylpropyl (2*R*,3*S*)-3-(3′-bromo-2′,5′-dimethoxyphenyl)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropionate

To a solution of the alcohol **19** (795.5 mg, 1.10 mmol) in anhydrous CH_2Cl_2 (10 mL) cooled at 0 °C was sequentially added 2,6-lutidine (0.25 mL, 2.20 mmol) and TBSOTf (0.4 mL, 1.60 mmol) under a nitrogen atmosphere. After stirring at 0 °C for 1 h, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ at 0 °C. The reaction mixture was then extracted with CH_2Cl_2 (15 mL×3). The combined organic layer was washed with brine,

dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 9.1% EtOAc in PE) to give the corresponding TBS ether (913.7 mg, 99%) as a colorless viscous oil. R_f=0.42 (9.1% EtOAc in PE); $[\alpha]_D^{20}$ −26.9 (*c* 0.62, $CHCl_3$); IR (film): 2955, 2931, 2857, 1744, 1605, 1515, 1463, 1251, 1154, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.38 (m, 2H), 7.32–7.23 (m, 3H), 7.19–7.15 (m, 1H), 7.08 (t, *J*=7.6 Hz, 2H), 7.00 (d, *J*=2.8 Hz, 1H), 6.87 (d, *J*=3.6 Hz, 1H), 6.87 (s, 2H), 6.73 (d, *J*=7.2 Hz, Hz, 2H), 5.69 (d, *J*=6.0 Hz, 1H), 5.11 (d, *J*=8.4 Hz, 1H), 4.86 and 4.41 (ABq, *J*=16.4 Hz, 2H), 4.09–4.01 (m, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 2.83–2.72 (br s, 1H), 2.41 (s, 6H), 2.31 (s, 3H), 1.18 (d, *J*=7.2 Hz, 3H), 0.81 (s, 9H), 0.78 (d, *J*=7.6 Hz, 3H), 0.02 (s, 3H), −0.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 156.2, 148.1, 142.4, 140.4 (×2), 138.6, 138.1, 137.9, 133.0, 132.1 (×2), 128.4 (×2), 128.4 (×2), 128.2 (×2), 127.8, 127.4, 126.4 (×2), 118.2, 117.0, 112.6 (br), 77.8, 71.0 (br), 61.2, 56.7, 55.7, 48.8 (br), 48.1, 25.8 (×3), 22.9 (×2), 20.9, 18.1, 14.8, 14.1, −4.7, −5.0; HRMS (+EI) calcd for $C_{43}H_{56}BrNO_7SSi$ 837.2730 (M^+), found 837.2738.

4.20. (2*S*,3*S*)-3-(3′-Bromo-2′,5′-dimethoxyphenyl)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropan-1-ol (20)

To a solution of the above TBS ether (1.510 g, 1.80 mmol) in anhydrous CH_2Cl_2 (20 mL) cooled at −78 °C was added DIBAL-H (1.0 M in hexane, 3.60 mL, 3.60 mmol) followed by stirring at the same temperature for 45 min. The reaction was quenched by careful addition of MeOH (5 mL) at −78 °C and the reaction mixture was allowed to warm to room temperature. A saturated aqueous solution of sodium potassium tartrate (20 mL) was added and the resultant mixture was stirred at room temperature for about 1 h. The mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 7.7% EtOAc in PE) to give **20** (739.8 mg, 98%) as a colorless oil. R_f=0.35 (7.7% EtOAc in PE); $[\alpha]_D^{20}$ −17.1 (*c* 0.41, $CHCl_3$); IR (film): 3428 (br), 1600, 1471, 1425, 1253, 1216, 1047, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J*=3.2 Hz, 1H), 6.98 (d, *J*=3.2 Hz, 1H), 5.05 (d, *J*=4.4 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.64–3.59 (m, 1H), 3.43–3.36 (m, 1H), 2.85 (t, *J*=6.0 Hz, 1H, OH), 2.06–1.93 (m, 1H), 0.97 (d, *J*=7.2 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 3H), −0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 147.2, 138.5, 117.7, 116.7, 112.5, 73.4 (br), 65.0, 61.1, 55.6, 42.0, 25.7 (×3), 18.0, 13.8, −4.7, −5.2; HRMS (+EI) calcd for $C_{18}H_{31}BrO_4Si$ 418.1175 (M^+), found 418.1177.

4.21. *N*-(1′*S*,2′*S*)-3-{1′-[(*tert*-Butyldimethylsilyl)oxy]-3′-hydroxy-2′-methylporpyl}-2,5-dimethoxyphenyl 2,2,2-trifluoroacetamide (21)

An over-dried Schlenk tube was charged with CuI (10.0 mg, 5.0×10^{-2} mmol), K_2CO_3 (276.4 mg, 2.00 mmol) and 4 Å MS (500 mg). The tube was evacuated and backfilled with nitrogen several times. Then, a solution of the aryl bromide **20** (419.4 mg, 1.00 mmol), 2,2,2-trifluoroacetamide (170.2 mg, 1.50 mmol), and *N*,*N*′-dimethylethylenediamine (12 μL, 0.10 mmol) in degassed anhydrous 1,4-dioxane (3.0 mL) was added under nitrogen through a syringe. The tube was heated at 100 °C for 45 h. The reaction mixture was cooled to room temperature and extracted with EtOAc (7 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 12.5% EtOAc in PE) to give **15** (374.8 mg, 83%) as a pale yellow oil. R_f=0.32 (14.3% EtOAc in PE); $[\alpha]_D^{20}$ −25.1 (*c* 0.32, $CHCl_3$); IR (film): 3405, 2956, 1733, 1543, 1471, 1210, 1157, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (br s, 1H, NH), 7.79 (d, *J*=2.8 Hz, 1H), 6.88 (d, *J*=2.8 Hz, 1H), 5.01 (d, *J*=5.2 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.68–3.60 (m, 1H), 3.50–3.40 (m, 1H), 2.63 (br s, 1H, OH), 2.04–1.94 (m, 1H), 0.96 (d, *J*=7.2 Hz, 3H), 0.92 (s, 9H), 0.12 (s, 3H), −0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 154.5 ($^2J_{C,F}$=37.0 Hz), 139.7, 137.2, 129.1, 115.6 ($^1J_{C,F}$=288.7 Hz), 110.3, 105.8, 72.9 (br), 65.1, 61.6, 55.7, 42.2, 25.8 (×3), 18.1, 14.0, −4.6, −5.1; HRMS (+EI) calcd for $C_{20}H_{32}F_3NO_5Si$ 451.2002 (M^+), found 451.1995.

4.22. *N*-(1′*S*,2′*S*)-3-{1′-[(*tert*-Butyldimethylsilyl)oxy]-2′-methyl-3′-oxoporpyl}-2,5-dimethoxyphenyl 2,2,2-trifluoroacetamide (22)

To a solution of **21** (451.6 mg, 1.00 mmol) in anhydrous CH_2Cl_2 (10 mL) was added powdered $NaHCO_3$ (840.0 mg, 10.00 mmol). Then, Dess–Martin periodinane (DMP, 1M in CH_2Cl_2, 2 mL, 2.00 mmol) was added dropwise at 0 °C followed by stirring at the same temperature for 30 min. The reaction mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (10 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 9.1% EtOAc in PE) to give **22** (427.1 mg, 95%) as a colorless oil. R_f=0.35 (9.1% EtOAc in PE); $[\alpha]_D^{20}$ −20.1 (*c* 0.37, $CHCl_3$); IR (film): 3406, 2933, 1730, 1543, 1472, 1427, 1209, 1156, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.37 (br s, 1H, NH), 7.82 (s, 1H), 6.86 (s, 1H), 5.13 (d, *J*=6.0 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.78–2.70 (m, 1H), 0.98 (d, *J*=6.8 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), −0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 156.5, 154.6 ($^2J_{C,F}$=36.6 Hz), 139.8, 136.3, 129.4, 115.6 ($^1J_{C,F}$=288.7 Hz), 110.0, 106.2, 70.5, 61.7, 55.7, 53.8, 25.7 (×3), 18.1, 11.1, −4.5, −5.1; HRMS (+EI) calcd for $C_{20}H_{30}F_3NO_5Si$ 449.1845 (M^+), found 449.1850.

4.23. *N*-(1′*S*,2′*S*)-5-{1′-[(*tert*-Butyldimethylsilyl)oxy]-2′-methyl-3′-oxoporpyl}-3,6-dioxocyclohexa-1,4-dienyl 2,2,2-trifluoroacetamide (23)

To a solution of **22** (54.1 mg, 0.12 mmol) in MeCN (5 mL) cooled in an ice–water bath (0 °C) with stirring was added dropwise a solution of cerium(IV) ammonium nitrate (CAN, 328.9 mg, 0.60 mmol) in H_2O (1 mL) followed by stirring at the same temperature for 15 min. The reaction mixture was then poured in H_2O (5 mL) and extracted with EtOAc (5 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 9.1% EtOAc in PE) to give **23** (46.3 mg, 92%) as a yellow solid. Mp 87–88 °C (CH_2Cl_2); R_f=0.32 (9.1% EtOAc in PE); $[\alpha]_D^{20}$ −49.8 (*c* 0.22, $CHCl_3$); IR (film): 3355, 2956, 2933, 1748, 1730, 1654, 1613, 1534, 1262, 1222, 1172, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, *J*=2.0 Hz, 1H), 8.77 (br s, 1H, NH), 7.60 (d, *J*=2.4 Hz, 1H), 6.86 (dd, *J*=2.4, 1.2 Hz, 1H), 5.00 (dd, *J*=4.0, 1.6 Hz, 1H), 2.65–2.57 (m, 1H), 1.18 (d, *J*=7.2 Hz, 3H), 0.92 (s, 9H), 0.13 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 186.3, 181.4, 155.4 ($^2J_{C,F}$=39.8 Hz), 146.4, 136.5, 134.6, 117.7, 114.7 ($^1J_{C,F}$=288.1 Hz), 69.3, 51.5, 25.6 (×3), 18.0, 11.3, −4.6, −5.2; HRMS (+EI) calcd for $C_{18}H_{24}F_3NO_5Si$ 419.1376 (M^+), found 419.1369.

Acknowledgements

The Laboratory of Asymmetric Catalysis and Synthesis is established under the Cheung Kong Scholars Program of The Ministry of Education of China. This work is supported in part by The National Natural Science Foundation of China (Grand No. 21372197).

Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra for the compounds **3b**, **6**, **7a**, **9**–**23** and the related intermediates.) related to

this article can be found at http://dx.doi.org/10.1016/j.tet.2015.05.052.

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