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Formal Total Synthesis of (−)-Apicularen A by a Strategy Based on Ring-Closing Metathesis and Transannular Cyclization

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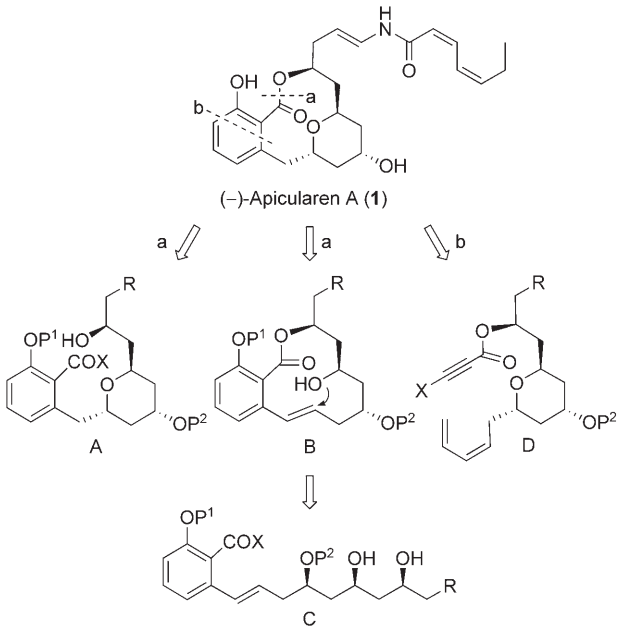
Abstract: A formal synthesis of (−)-apicularen A, a potent antitumor agent with unique biological properties, has been completed in a 15-step sequence starting from a known, enantiomerically pure hydroxyepoxide, which was generated by using the Jacobsen hydrolytic-kinetic-resolution methodology. The 12-membered macrocyclic lactone in the target was constructed by ring-closing metathesis, and the *trans*-tetrahydropyran ring system was created through the transannular etherification of a hydroxyalkene.

Keywords: hydrolytic kinetic resolution · metathesis · natural products · total synthesis · transannular cyclization

Introduction

Apicularen A displays potent antitumor activity against several human cancer cell lines.[1] The biological properties of this natural product differ from those of other known antitumor agents in that it shows antiangiogenesis activity[2] and inhibits mammalian V-ATPase.[3] In addition to its unique biological properties, apicularen A has intriguing structural characteristics, which include a macrocyclic salicylate ester core skeleton, an embedded *trans*-tetrahydropyran ring, and an enamide side chain. Owing to these biological and structural features, apicularen A has attracted much synthetic interest. Several total syntheses and formal total syntheses have been reported,[4] and a number of synthetic methods have been developed for the construction of its bicyclic core structure.[5]

Major issues associated with the synthesis of apicularen A are the construction of the macrocyclic lactone and the stereocontrolled synthesis of the embedded *trans*-tetrahydropyran ring system. As shown in Scheme 1, two general strategies (macrolactonization (path a) and an intramolecular Diels–Alder reaction (path b)) have been employed for the generation of the macrocyclic lactone. A lactone-formation strategy that makes use of the *trans*-tetrahydropyran-containing benzoic acid derivative A has been utilized by several research groups.[4b–d,5a,b,f] Syntheses of the 12-membered lactone B by the macrolactonization of C have also been reported.[4e,5c,h] Subsequent acid- or base-catalyzed transannular cyclizations were used to generate the *trans*-tetrahydropyran ring. Similarly, the transannular conjugate addition of



Scheme 1. Known synthetic strategies for (−)-apicularen A (**1**). P^1 and P^2 are protecting groups.

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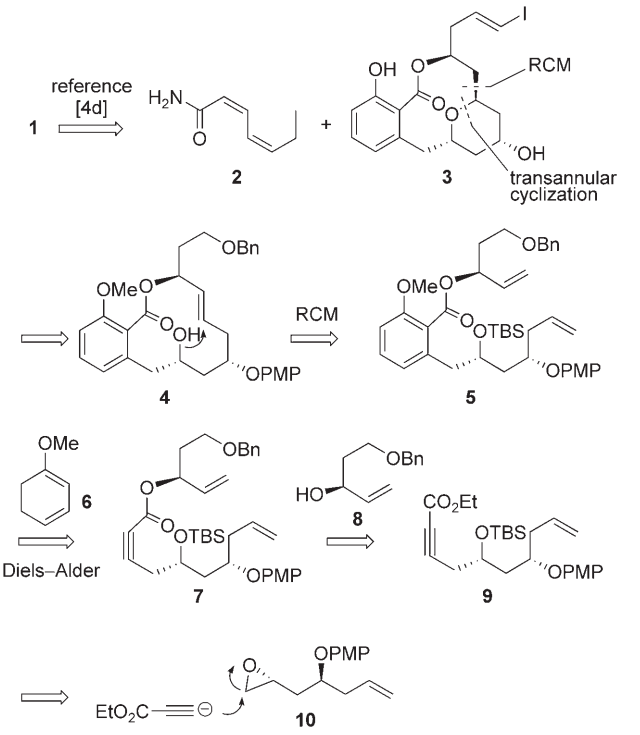
a macrocyclic hydroxyenone served as another method for the introduction of the *trans*-tetrahydropyran ring system.[5d,g] The intramolecular Diels–Alder reaction of the functionalized *trans* tetrahydropyran D is yet another strategy that has been used for the synthesis of the 10-membered macrocyclic lactone ring of apicularen A.[5e]

Although ring-closing metathesis (RCM)[6] has been used on numerous occasions for the synthesis of naturally occurring macrocyclic lactones,[7] this methodology has not yet been applied to the synthesis of apicularen A. Herein, we describe a formal total synthesis of this antitumor agent in which an RCM reaction is used for the construction of an advanced intermediate with a 12-membered macrocyclic lactone core.

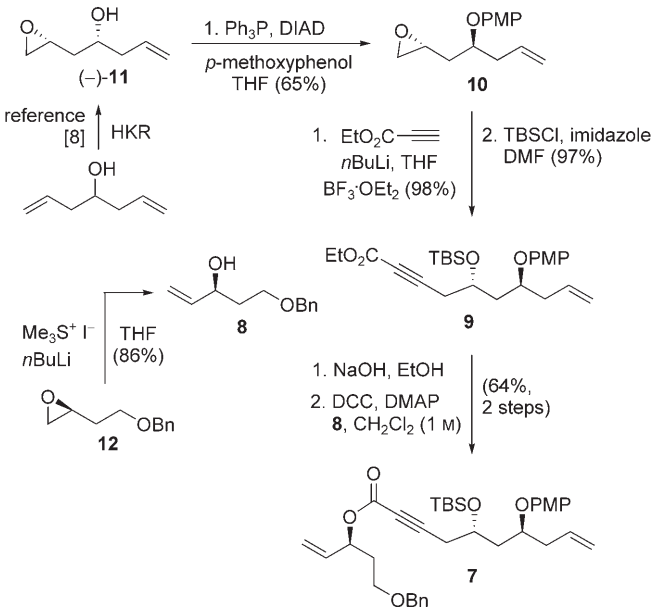
Results and Discussion

The target of our effort was the vinyl iodide **3**,[4c,d,5e] which Su and Panek[4d] coupled successfully with the amide **2** in their synthesis of the natural product (Scheme 2). We envisaged that the *trans*-tetrahydropyran ring system in **3** could be installed by a transannular etherification of the intermediate macrocyclic lactone **4**, which itself could be obtained by ring-closing metathesis of the diene **5**. We planned to prepare the salicylate **5** from the alkynoate **7** and 1,3-diene **6** through a Diels–Alder/retro-Diels–Alder reaction sequence. The desired configuration at the three stereocenters in **7** is already present in the allylic alcohol and enyne precursors **8** and **9**. The *anti*-1,3-diol moiety in the latter substance would result from nucleophilic epoxide-ring opening of **10**.

The route to apicularen A based on the strategy outlined above starts with the hydroxyepoxide (−)-**11**, which we had prepared previously[8] by using the method for hydrolytic kinetic resolution (HKR) described by Jacobsen and co-workers.[9] Mitsunobu inversion of **11** with *p*-methoxyphenol afforded the PMP-protected *anti* epoxide **10** (Scheme 3), which was converted into the enynoate ester **9** in high yield



Scheme 2. Retrosynthesis of (−)-apicularen A (**1**). Bn = benzyl, PMP = *p*-methoxyphenyl, TBS = *tert*-butyldimethylsilyl.



Scheme 3. Synthesis of the precursor **7** for the Diels–Alder reaction. DCC = *N*,*N*′-dicyclohexylcarbodiimide, DIAD = diisopropylazodicarboxylate, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide.

by treatment with the lithium acetylide of ethyl propynoate in the presence of $BF_3{\cdot}OEt_2$ followed by protection of the resulting alcohol with TBSCl. The required allylic alcohol (*S*)-**8** was synthesized in 86% yield by the reported proce-

Abstract in Korean:
독특한 생활성 특성으로 강한 항암작용을 나타내는 것으로 알려진 (-)-에피큘라렌-A 의 포멀 전합성을 알려진 이폭사이드로부터 15 단계에 완성하였다. 제이콥슨의 가수분해 동력학 분리(HKR) 방법을 이용해 만든 광학적으로 순수한 하이드록시 이폭사이드의 고리열림반응으로 하이드록시 테트라하이드로피렌의 1,3-다이올구조 입체화학을 결정하였다. 12-원환 거대고리 락톤구조는 올레핀상호교환고리화 반응으로 만들 수 있었고 *트렌스*-테트라하이드로피렌 고리 구조는 하이드록시 알켄의 트랜스애뉼러 이써화 반응으로 완성하였다.

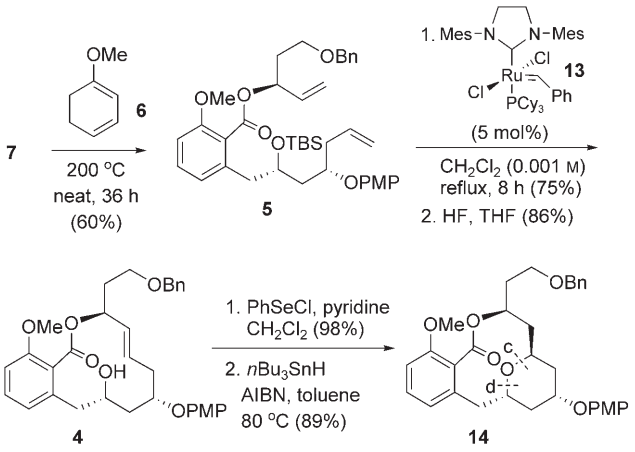
dure[10] involving treatment of the known *S* epoxide **12** (available from (*S*)-malic acid[11] or through the hydrolytic kinetic resolution of racemic **12**[12]) with dimethylsulfonium methylide. Saponification of the ethyl ester **9** with aqueous NaOH in EtOH gave the corresponding acid in quantitative yield. An exploration of coupling conditions (Table 1) showed that **7** is obtained in an optimum yield of 68% when the alkynoic acid is treated as a 1 M solution in CH_2Cl_2 with the alcohol **8** in the presence of DCC/DMAP[13] (Table 1, entry 2).

Table 1. Conditions examined for the coupling reaction to give **7**.

Entry	Reagents and conditions	Yield [%]
1	DCC, cat. DMAP, CH_2Cl_2 (0.25 M), 10 h	28
2	DCC, cat. DMAP, CH_2Cl_2 (1.00 M), 44 h	68
3	DCC, HOBT,[a] cat. DMAP, CH_2Cl_2 (0.25 M), 10 h	17
4	EDC,[b] cat. DMAP, CH_2Cl_2 (0.25 M), 10 h	21
5	$(COCl)_2$, pyridine, CH_2Cl_2 (0.10 M), 2 h	36
6	$(COCl)_2$, Et_3N, CH_2Cl_2 (0.10 M), 2 h	17
7	$SOCl_2$, pyridine, CH_2Cl_2 (0.10 M), 2 h	31

[a] HOBT = 1-hydroxybenzotriazole. [b] EDC = *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide.

With the alkynoate **7** in hand, we next investigated its Diels–Alder reaction with 1-methoxycyclohexa-1,3-diene (**6**).[14] The reaction was most efficient when carried out at 200 °C without solvent. Under these conditions, the ensuing retro-Diels–Alder reaction with the loss of ethylene occurred to provide **5** in 60% yield without the formation of the other regioisomeric product (Scheme 4). The macrolac-

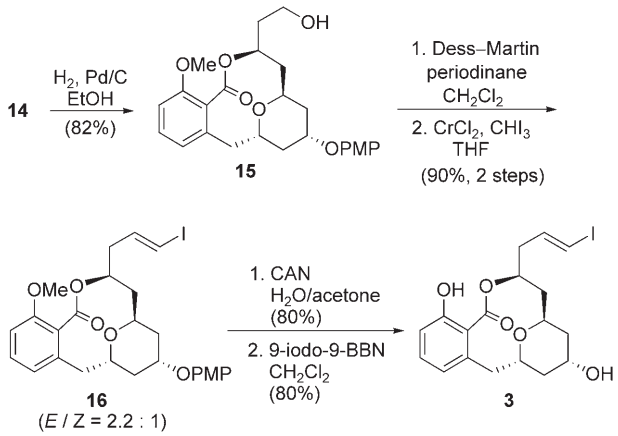


Scheme 4. Macrolactone synthesis by an RCM–transannular-cyclization sequence. AIBN = azobisisobutyronitrile, Cy = cyclohexyl, Mes = mesityl.

tonization of **5** by ring-closing metathesis occurred in the presence of the second-generation Grubbs catalyst **13** (5 mol%) at reflux in CH_2Cl_2 (0.001 M) to give the 12-membered lactone in 75% yield. Removal of the TBS group with HF in THF then generated the alcohol **4**. The *trans* geometry of the alkene in **4** was determined from the coupling constant ($J = 15.1$ Hz) between the vinyl hydrogen atoms.

The next key transformation in the synthetic sequence was the transannular cyclization to install the embedded *trans*-tetrahydropyran ring system. The cyclization pathway (disconnection c; see **14** in Scheme 4) used in this sequence differs from those described previously (disconnection d).[4e, 5g, h] In contrast to mercury(II)-promoted cyclizations of the alcohol–alkene moiety with $Hg(OAc)_2$ and $Hg(OTFA)_2$ (TFA = trifluoroacetyl), which did not give the desired product, the treatment of **4** with phenylselenyl chloride[15] provided the desired *trans* tetrahydropyran as a single isomer in 98% yield. The reductive removal of the phenylselenyl group with tributyltin hydride yielded **14**. The expected *trans* configuration of the tetrahydropyran ring in this intermediate was confirmed by the completion of the formal synthesis of apicularen A.

The remaining steps in the route to the *trans* vinyl iodide **3** are shown in Scheme 5. The oxidation of the alcohol **15**, which was produced by hydrogenolytic removal of the



Scheme 5. Completion of the formal synthesis of (−)-apicularen A. 9-BBN = 9-borabicyclo[3.3.1]nonane, CAN = ceric ammonium nitrate.

benzyl group in **14**, with SO_3/pyridine (dimethyl sulfoxide, Et_3N, CH_2Cl_2) or under conditions of ruthenium catalysis (catalytic tetrapropylammonium perruthenate (TPAP), 4-methylmorpholine *N*-oxide, 4-Å molecular sieves, CH_2Cl_2) led to difficulties in the purification steps as a result of the decomposition of the labile β-alkoxy aldehyde. Therefore, we found it best to subject the aldehyde obtained by Dess–Martin oxidation of **15**, aqueous $NaHCO_3$ workup, and flash column chromatography, to the Takai iodoolefination ($CrCl_2$ and CHI_3 in THF) directly.[16] In this way, the *E* vinyl iodide **16** was produced as the major product ($E/Z = 2.2{:}1$) in 90% yield for the two steps.

Removal of the *p*-methoxyphenyl group in **16** with ceric ammonium nitrate in aqueous acetone followed by demethylation with 9-iodo-9-BBN[7f] afforded the target substance **3**. The optical rotation ($[\alpha]_D^{23} = -48$ ($c = 0.7$, acetone) (reference [4d]: $[\alpha]_D^{23} = -46$ ($c = 0.75$, acetone))) and NMR spectroscopic properties (^{1}H NMR, ^{13}C NMR)[5e] of **3** are identi-

cal to those reported previously. Su and Panek used a copper(I) thiophene carboxylate[17] catalyzed coupling reaction of **3** with the amide **2** to complete their total synthesis of (−)-apicularen A.[4d]

Conclusions

In conclusion, we have completed a formal total synthesis of (−)-apicularen A that relies on a key RCM reaction to form the macrocyclic lactone and a transannular alcohol–alkene cyclization to construct the *trans*-tetrahydropyran ring system. The *anti*-1,3-diol precursor to the hydroxy-substituted tetrahydropyran ring in apicularen A was derived from an optically pure hydroxy epoxide formed by hydrolytic kinetic resolution.

Experimental Section

General Methods

THF and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen immediately prior to use. For CH_2Cl_2, toluene, and benzene, the drying agent used was calcium hydride. All reactions were carried out under a nitrogen atmosphere. All chromatographic purifications were performed on silica gel (230–400 mesh) with the solvent systems indicated. All recorded melting points are uncorrected. NMR spectra were recorded with reference to tetramethylsilane as an internal standard. Organic extracts were dried over anhydrous $MgSO_4$.

Syntheses

8: *n*BuLi (1.6 M, 0.84 mL) was added to a solution of trimethylsulfonium iodide (274 mg, 1.34 mmol) in THF (3.4 mL) at −20 °C, and the resulting mixture was stirred for 30 min. A solution of **12** (80 mg, 0.447 mmol) in THF (1.1 mL) was then added at −20 °C, and the reaction mixture was stirred for 1 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/ethyl acetate = 5:1) yielded **8** (74 mg, 86 %) as a colorless oil. R_f = 0.24 (silica gel, hexane/ethyl acetate = 3:1); $[\alpha]_D^{23}$ = 11.5 (c = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3433, 2957, 2979, 2860, 1725, 1454, 1365, 1275, 1205, 1098, 1075, 1027 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5H), 5.87–5.78 (m, 1H), 5.24 (d, J = 17.2 Hz, 1H), 5.13 (d, J = 10.4 Hz, 1H), 4.49 (s, 2H), 4.31–4.29 (m, 1H), 3.69–3.57 (m, 2H), 3.15 (s, 1H), 1.85–1.77 ppm (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 140.6, 137.9, 128.4, 127.71, 127.69, 114.3, 73.2, 71.5, 68.1, 36.3 ppm; HRMS: m/z calcd for $C_{12}H_{16}O_2$: 193.1229 $[M+H]^+$; found: 193.1225.

10: DIAD (0.06 mL, 0.293 mmol) was added to a solution of (−)-**11** (25 mg, 0.195 mmol), Ph_3P (77 mg, 0.294 mmol), and *p*-methoxyphenol (73 mg, 0.588 mmol) in THF (0.65 mL) at room temperature, and the resulting mixture was stirred for 8 h. The solvent was then removed in vacuo, and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 15:1) to give **10** (29.7 mg, 65 %) as a colorless oil. R_f = 0.46 (silica gel, hexane/ethyl acetate = 5:1); $[\alpha]_D^{23}$ = 38.8 (c = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3072, 3047, 2999, 2925, 2834, 1730, 1641, 1506, 1465, 1441, 1359, 1227, 1106, 1037 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 6.93–6.80 (m, 4H), 5.92–5.73 (m, 1H), 5.13–5.07 (m, 2H), 4.41–4.39 (m, 1H), 3.76 (s, 3H), 3.13–3.09 (m, 1H), 2.79 (t, J = 4.8 Hz, 1H), 2.54–2.51 (m, 1H), 2.47–2.42 (m, 2H), 2.02–1.93 (m, 1H), 1.70–1.64 ppm (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 154.3, 152.2, 133.7, 118.0, 117.9, 114.7, 76.7, 55.7, 49.6, 47.7, 38.7, 37.6 ppm; HRMS: m/z calcd for $C_{14}H_{18}O_3$: 234.1256 $[M]^+$; found: 234.1260.

9: *n*BuLi (10.88 mL, 17.5 mmol) was added to a solution of ethyl propiolate (1.76 mL, 17.5 mmol) in THF (50 mL) at −78 °C, and the resulting mixture was stirred for 30 min. A solution of **10** (1.36 g, 5.80 mmol) in THF (8 mL) and $BF_3{\cdot}OEt_2$ (2.2 mL, 17.5 mmol) were then added at −78 °C, and the reaction mixture was stirred for 1 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (100 mL), and the aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/ethyl acetate = 10:1–5:1) yielded the alcohol (1.89 g, 98 %) as a colorless oil. R_f = 0.49 (silica gel, hexane/ethyl acetate = 3:1); $[\alpha]_D^{23}$ = 37.1 (c = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3485, 2951, 2236, 1709, 1506, 1466, 1442, 1367, 1252, 1227, 1072, 1037 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 6.91–6.79 (m, 4H), 5.80–5.73 (m, 1H), 5.13–5.06 (m, 2H), 4.50–4.47 (m, 1H), 4.23–4.15 (m, 3H), 3.75 (s, 3H), 3.09–3.07 (m, 1H), 2.54–2.50 (m, 2H), 2.50–2.35 (m, 2H), 1.86–1.80 (m, 2H), 1.28 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 154.2, 153.7, 151.9, 133.5, 118.0, 117.7, 114.7, 85.9, 75.4, 75.0, 66.1, 62.0, 55.6, 40.3, 38.2, 28.0, 14.0 ppm. TBSCl (1.28 g, 8.49 mmol) was added to a solution of the alcohol (1.89 g, 5.68 mmol), imidazole (772 mg, 11.3 mmol), and DMAP (cat.) in DMF (4 mL) at room temperature, and the resulting mixture was stirred for 5 h. The reaction was then quenched with saturated aqueous NH_4Cl (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/ethyl acetate = 30:1) yielded **9** (2.46 g, 97 %) as a colorless oil. R_f = 0.56 (silica gel, hexane/ethyl acetate = 5:1); $[\alpha]_D^{23}$ = 25.9 (c = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}$ = 2955, 2930, 2857, 2357, 2237, 1714, 1506, 1464, 1367, 1252, 1228, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.81 (s, 4H), 5.84–5.74 (m, 1H), 5.11–5.07 (m, 2H), 4.38–4.32 (m, 1H), 4.2 (q, J = 7.0 Hz, 2H), 4.14–4.08 (m, 1H), 3.76 (s, 3H), 2.52 (d, J = 5.7 Hz, 2H), 2.48–2.42 (m, 1H), 2.38–2.31 (m, 1H), 1.97–1.91 (m, 1H), 1.86–1.79 (m, 1H), 1.30 (t, J = 7.2 Hz, 3H), 0.85 (s, 9H), 0.02 (s, 3H), −0.12 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9, 153.8, 151.8, 133.6, 118.0, 117.1, 114.8, 86.1, 75.1, 73.7, 67.1, 61.9, 55.8, 42.1, 38.0, 28.5, 25.9, 18.1, 14.2, −4.2, −4.7 ppm; HRMS: m/z calcd for $C_{25}H_{38}O_5Si$: 446.2489 $[M]^+$; found: 446.2490.

7: NaOH (1 N, 61 mL, 61 mmol) was added to a solution of **9** (2.74 g, 6.13 mmol) in EtOH (61 mL) at 0 °C, and the resulting mixture was stirred for 1 h. The reaction was quenched with HCl (0.5 N) to pH 5–6. Removal of the solvent in vacuo and purification by chromatography on silica gel (CH_2Cl_2/MeOH = 10:1) yielded the alkynoic acid (2.41 g, 94 %) as a colorless oil. R_f = 0.56 (silica gel, CH_2Cl_2/MeOH = 5:1); $[\alpha]_D^{23}$ = 10.7 (c = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3475, 2954, 2928, 2857, 2240, 1727, 1588, 1506, 1463, 1382, 1227, 1107, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.82 (s, 4H), 5.83–5.77 (m, 1H), 5.12–5.08 (m, 2H), 4.38–4.34 (m, 1H), 4.16–4.11 (m, 1H), 3.77 (s, 3H), 2.57–2.56 (m, 2H), 2.57–2.55 (m, 1H), 2.39–2.34 (m, 1H), 1.96–1.83 (m, 2H), 0.86 (s, 9H), 0.03 (s, 3H), −0.11 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 154.0, 151.8, 133.5, 118.1, 117.1, 114.8, 89.1, 74.6, 73.8, 67.1, 55.9, 42.1, 37.9, 28.6, 25.9, 18.1, −4.2, −4.7 ppm. Solutions of the alkynoic acid (1.70 g, 4.07 mmol) in CH_2Cl_2 (2 mL) and DCC (924 mg, 4.48 mmol) in CH_2Cl_2 (1 mL) were added to a solution of **8** (822 mg, 4.27 mmol) and DMAP (99 mg, 0.81 mmol) in CH_2Cl_2 (1 mL) at 0 °C, and the reaction mixture was stirred for 44 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/ethyl acetate = 20:1) yielded **7** (1.64 g, 68 %) as a colorless oil. R_f = 0.62 (silica gel, hexane/ethyl acetate = 3:1); $[\alpha]_D^{23}$ = 14.4 (c = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3469, 2928, 2856, 2238, 1712, 1630, 1506, 1463, 1360, 1249, 1228, 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.34 (m, 4H), 7.30–7.28 (m, 1H), 6.83 (s, 4H), 5.86–5.78 (m, 2H), 5.53 (q, J = 6.6 Hz, 1H), 5.31 (d, J = 17.2 Hz, 1H), 5.22 (d, J = 10.5 Hz, 1H), 5.12 (s, 1H), 5.09–5.08 (m, 1H), 4.50 (s, 2H), 4.38–4.36 (m, 1H), 4.14–4.11 (m, 1H), 3.77 (s, 3H), 3.55 (t, J = 6.2 Hz, 2H), 2.53 (d, J = 5.4 Hz, 2H), 2.45–2.43 (m, 1H), 2.38–2.36 (m, 1H), 2.04–1.91 (m, 3H), 1.88–1.85 (m, 1H), 0.89 (s, 9H), 0.04 (s, 3H), −0.10 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9, 152.9, 151.8, 138.3, 135.6, 133.5,

128.5, 127.8, 127.7, 118.0, 117.7, 117.0, 114.8, 86.4, 75.0, 73.9, 73.7, 73.2, 67.1, 66.0, 55.8, 42.2, 37.9, 34.4, 28.6, 25.9, 18.1, −4.2, −4.7 ppm; HRMS: *m/z* calcd for $C_{35}H_{48}O_6Si$: 592.3220 $[M]^+$; found: 592.3221.

5: Argon was bubbled through a solution of **7** (492 mg, 0.829 mmol) in **6** (2 mL, 65%, 10.9 mmol) for 20 min at room temperature. The reaction mixture was then heated in a sealed glass tube for 36 h at 190–200 °C. The solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 30:1) to give **5** (336 mg, 60%) as a colorless oil. R_f = 0.21 (silica gel, hexane/ethyl acetate = 8:1); $[\alpha]_D^{23} = -0.7$ (c = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3428, 2950, 2930, 2856, 1728, 1585, 1506, 1471, 1362, 1269, 1228, 1111, 1075, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 6H), 6.91 (d, J = 7.7 Hz, 1H), 6.82–6.78 (m, 5H), 5.91–5.74 (m, 3H), 5.42 (d, J = 17.3 Hz, 1H), 5.20 (d, J = 10.5 Hz, 1H), 5.13–5.07 (m, 2H), 4.55 (q, J = 13.2 Hz, 2H), 4.35 (m, 1H), 4.21 (m, 1H), 3.76 (s, 6H), 3.66–3.64 (m, 2H), 2.85–2.83 (m, 1H), 2.77–2.73 (m, 1H), 2.43–2.41 (m, 1H), 2.35–2.34 (m, 1H), 2.13–2.10 (m, 1H), 2.06–2.04 (m, 1H), 1.84–1.81 (m, 1H), 1.76–1.72 (m, 1H), 0.87 (s, 9H), −0.12 (s, 3H), −0.18 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 156.4, 153.7, 151.9, 138.4, 137.1, 136.1, 133.9, 129.9, 128.4, 127.6, 127.5, 124.6, 123.1, 117.6, 117.3, 117.2, 114.5, 109.0, 74.2, 73.1, 73.0, 69.5, 66.3, 55.7, 55.6, 42.0, 41.7, 38.0, 34.6, 26.0, 18.0, −4.5, −4.8 ppm; HRMS: *m/z* calcd for $C_{40}H_{54}O_7Si$: 674.3639 $[M]^+$; found: 674.3647.

4: The ruthenium complex **13** (5 mol%) was added to a solution of **5** (408 mg, 0.600 mmol) in CH_2Cl_2 (200 mL), and the resulting mixture was heated under reflux at 50 °C for 8 h under argon. The solvent was then removed in vacuo, and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 20:1) to give the macrocyclic lactone (293 mg, 75%) as a colorless oil. R_f = 0.20 (silica gel, hexane/ethyl acetate = 8:1); $[\alpha]_D^{23} = -118$ (c = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3407, 2946, 2929, 2855, 1721, 1582, 1506, 1471, 1439, 1360, 1264, 1226, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.33 (m, 3H), 7.29–7.25 (m, 2H), 7.20 (t, J = 8.0 Hz, 1H), 6.86–6.84 (m, 4H), 6.77 (t, J = 7.4 Hz, 2H), 6.26–6.21 (m, 1H), 5.89–5.80 (m, 2H), 4.56 (q, J = 11.2 Hz, 2H), 4.24–4.22 (m, 1H), 3.96–3.94 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.60–3.57 (m, 2H), 3.33–3.31 (m, 1H), 2.72–2.69 (m, 1H), 2.34–2.28 (m, 1H), 2.25–2.17 (m, 2H), 2.09–2.04 (m, 2H), 2.00–1.94 (m, 1H), 0.68 (s, 9H), −0.10 (s, 3H), −0.50 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 156.3, 154.3, 151.4, 138.5, 137.9, 133.2, 133.1, 129.7, 128.5, 127.8, 127.7, 125.6, 123.8, 117.7, 115.0, 109.4, 77.4, 73.4, 72.9, 68.4, 66.5, 56.2, 55.9, 47.0, 40.1, 36.6, 33.7, 25.8, 17.9, −5.0, −5.7 ppm; HRMS: *m/z* calcd for $C_{38}H_{50}O_7Si$: 647.3404 $[M+H]^+$; found: 647.3400. HF–pyridine (1.12 mL, 70%, 0.4 M) was added to a solution of the lactone (293 mg, 0.453 mmol) in THF (15 mL) at 0 °C, and the resulting mixture was stirred for 10 h at room temperature. The reaction mixture was then neutralized with saturated aqueous $NaHCO_3$ at 0 °C, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/ethyl acetate = 3:1) yielded **4** (159 mg, 66%) as a colorless oil; $[\alpha]_D^{23} = -41.6$ (c = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3448, 2927, 2848, 1719, 1581, 1506, 1470, 1438, 1264, 1224, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.23 (m, 6H), 6.88–6.79 (m, 6H), 6.28 (ddd, J = 5.6, 9.3, 15.1 Hz, 1H), 5.85–5.73 (m, 2H), 4.55–4.47 (m, 3H), 4.22–4.18 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.64–3.58 (m, 2H), 3.31–3.28 (m, 1H), 2.61 (ddd, J = 6.0, 6.3, 13.1 Hz, 1H), 2.41 (dd, J = 11.6, 13.6 Hz, 1H), 2.25–2.17 (m, 3H), 2.11–2.04 (m, 1H), 1.87 ppm (dd, J = 4.3, 14.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 156.8, 154.5, 151.1, 138.4, 137.9, 134.4, 131.9, 130.4, 128.5, 127.8, 127.7, 124.2, 123.0, 117.9, 114.9, 109.8, 77.04, 73.3, 73.0, 68.0, 66.5, 56.0, 55.7, 42.7, 40.9, 37.5, 33.7 ppm; HRMS: *m/z* calcd for $C_{32}H_{36}O_7$: 532.2461 $[M]^+$; found: 532.2463.

14: PhSeCl (12 mg, 0.060 mmol) was added to a solution of **4** (30 mg, 0.056 mmol) and pyridine (0.060 mL, 0.060 mmol) in CH_2Cl_2 (0.30 mL) at 0 °C, and the resulting mixture was stirred for 3 h at room temperature. More PhSeCl (12 mg, 0.060 mmol) was then added at 0 °C, and the reaction mixture was stirred for a further 3 h at room temperature. The mixture was washed with HCl (1 N) then neutralized with saturated aqueous $NaHCO_3$ (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/ethyl acetate = 5:1–3:1) yielded the cyclized product (38 mg, 98%) as a white solid. Bu_3SnH (0.0084 mL, 0.032 mmol) was added to a solution of the selenide (9 mg, 0.013 mmol) and AIBN (cat.) in toluene (1 mL) at room temperature, and the resulting mixture was heated under reflux at 80 °C for 30 min. The reaction mixture was then cooled to room temperature, CCl_4 (0.50 mL) was added, and the resulting mixture was stirred for 1 h. Saturated aqueous KF (1 mL) was then added, and the aqueous layer was extracted with CH_2Cl_2 (2 × 1 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/ethyl acetate = 5:1–4:1) yielded **14** (6.2 mg, 89%) as a colorless oil. $[\alpha]_D^{23} = -7.4$ (c = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3391, 2928, 2860, 1717, 1578, 1506, 1468, 1437, 1362, 1271, 1228, 1093, 1070, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.20 (m, 6H), 6.88–6.81 (m, 4H), 6.75 (dd, J = 8, 11.5 Hz, 2H), 5.83–5.75 (m, 1H), 4.60–4.49 (m, 3H), 4.45–4.39 (m, 1H), 4.05–4.00 (m, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 3.67–3.63 (m, 2H), 3.58 (dd, J = 10.9, 14.5 Hz, 1H), 2.38 (dd, J = 1.1, 14.5 Hz, 1H), 2.11–2.05 (m, 1H), 19.4 (dd, J = 6.3, 13.1 Hz, 2H), 1.88–1.81 (m, 2H), 1.80–1.77 (m, 2H), 1.63–1.58 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 155.9, 154.3, 151.2, 138.9, 138.6, 130.1, 128.6, 127.9, 127.7, 125.8, 122.9, 117.7, 114.9, 109.4, 73.9, 73.5, 71.4, 70.9, 66.5, 65.8, 55.9, 40.0, 38.7, 36.2, 35.3, 34.1 ppm; HRMS: *m/z* calcd for $C_{32}H_{36}O_7$: 533.2539 $[M+H]^+$; found: 533.2531.

15: Pd/C (10%; 2 mg, 0.0019 mmol) was added to a solution of **14** (6 mg, 0.011 mmol) in EtOH (0.15 mL) at room temperature, and the resulting mixture was stirred for 1 h under H_2. The reaction mixture was then filtered, the solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 1:1–1:2) to give **15** (4 mg, 82%) as a colorless oil. $[\alpha]_D^{23} = 36$ (c = 0.60, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3546, 3446, 2931, 2357, 1719, 1580, 1506, 1468, 1438, 1360, 1271, 1228, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.24 (m, 1H), 6.87–6.82 (m, 4H), 6.81–6.77 (m, 2H), 5.76 (tt, J = 3.1, 10.8 Hz, 1H), 4.53–4.49 (m, 1H), 4.44–4.38 (m, 1H), 4.02–3.96 (m, 1H), 3.86–3.83 (m, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 3.58 (dd, J = 11.0, 14.5 Hz, 1H), 2.79–2.77 (m, 1H), 2.39 (dd, J = 1.6, 14.5 Hz, 1H), 2.13–2.07 (m, 1H), 1.97–1.75 (m, 5H), 1.63–1.59 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 155.5, 154.3, 151.1, 139.0, 130.5, 125.2, 123.0, 117.6, 114.9, 109.3, 74.1, 73.9, 71.3, 65.7, 60.8, 55.82, 55.77, 40.4, 38.5, 37.3, 36.3, 33.8 ppm; HRMS: *m/z* calcd for $C_{25}H_{30}O_7$: 443.2070 $[M+H]^+$; found: 443.2069.

16: Dess–Martin periodinane (8 mg, 0.018 mmol) was added to a solution of **15** (2 mg, 0.0045 mmol) in CH_2Cl_2 (0.05 mL) at room temperature, and the resulting mixture was stirred for 2 h. Saturated aqueous $NaHCO_3$ (1 mL) was then added, and the aqueous layer was extracted with ethyl acetate (2 × 1 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/ethyl acetate = 5:1) yielded the aldehyde as a yellow oil. A solution of anhydrous $CrCl_2$ (6.6 mg, 0.054 mmol, flame-dried under argon) in freshly distilled THF (0.5 mL) was stirred for 30 min at room temperature. The resulting creamy gray-green suspension was cooled to 0 °C, and a solution of the aldehyde and iodoform (7 mg, 0.018 mmol) in dry THF (1 mL) was added with a syringe. The reaction mixture was stirred for 1 h at 0 °C, then saturated brine (5 mL) was added, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/ethyl acetate = 5:1) yielded the *E* vinyl iodide **16** (1.6 mg, 62%) and the *Z* vinyl iodide (0.7 mg, 28%) as colorless solids. **16** (*E* vinyl iodide): M.p.: 142–144 °C; $[\alpha]_D^{23} = -33$ (c = 1.2, CCl_4); IR (film): $\tilde{\nu}$ = 3451, 2922, 1720, 1580, 1506, 1468, 1438, 1271, 1227, 1093, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.21 (m, 1H), 6.87–6.79 (m, 5H), 6.74 (d, J = 7.6 Hz, 1H), 6.60 (dt, J = 7.2, 14.4 Hz, 1H), 6.21 (d, J = 14.5 Hz, 1H), 5.65–5.60 (m, 1H), 4.52–4.51 (m, 1H), 4.43–4.37 (m, 1H), 4.04–3.99 (m, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.57 (dd, J = 11.0, 14.6 Hz, 1H), 2.47–2.29 (m, 3H), 2.12–2.04 (m, 1H), 1.87–1.77 (m, 4H), 1.61–1.57 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 156.0, 154.2, 151.1, 141.3, 138.8, 130.3, 125.5, 122.8, 117.6, 114.9, 109.5, 77.9, 73.9, 71.7, 71.3, 65.4, 56.1, 55.8, 41.0, 39.5, 38.6, 36.1, 34.0 ppm; HRMS: *m/z* calcd for $C_{26}H_{29}IO_6$: 565.1088 $[M+H]^+$; found: 565.1085. *Z* vinyl iodide: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.21 (m, 1H), 6.87–6.79 (m, 5H), 6.74 (d, J = 7.7 Hz, 1H), 6.39–6.32 (m, 2H), 5.71–5.65 (m, 1H), 4.52–4.49 (m, 1H), 4.43–4.37

(m, 1H), 4.05–4.00 (m, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.54 (dd, J=10.8, 14.6 Hz, 1H), 2.52 (t, J=6.2 Hz, 2H), 2.41–2.37 (m, 1H), 2.12–2.06 (m, 1H), 1.97–1.88 (m, 1H), 1.84–1.77 (m, 3H), 1.65–1.62 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.7, 155.9, 154.3, 151.1, 138.9, 137.0, 130.3, 125.6, 122.9, 117.6, 114.9, 109.6, 84.8, 73.8, 72.1, 71.3, 65.9, 56.1, 55.8, 40.2, 39.3, 38.7, 36.2, 34.2 ppm.

3: A solution of **16** (25 mg, 0.044 mmol) in acetone (0.88 mL) was added to a solution of ceric ammonium nitrate (36 mg, 0.066 mmol) in water (0.22 mL) at 0 °C, and the resulting mixture was stirred for 1 h at room temperature. More ceric ammonium nitrate (25 mg, 0.044 mmol) was added at 0 °C, and the reaction mixture was stirred for a further 1 h at room temperature. The reaction was quenched with water (5 mL), and the aqueous layer was extracted with diethyl ether (2×5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/ethyl acetate=1:1) yielded the secondary alcohol (16 mg, 80%) as a colorless solid. $[\alpha]_D^{23}=-48$ (c=1.1, $CHCl_3$); IR (film): $\tilde{\nu}$=3435, 2924, 1723, 1580, 1468, 1269, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.23 (t, J=8 Hz, 1H), 6.79 (d, J=8.3 Hz, 1H), 6.74 (d, J=7.6 Hz, 1H), 6.59 (dt, J=7.2, 14.4 Hz, 1H), 6.20 (d, J=14.5 Hz, 1H), 5.58 (m, 1H), 4.32–4.31 (m, 1H), 4.04–3.95 (m, 2H), 3.85 (s, 3H), 3.39 (dd, J=10.1, 15.0 Hz, 1H), 2.47–2.29 (m, 3H), 2.01–1.95 (m, 1H), 1.93–1.84 (m, 2H), 1.79–1.70 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.1, 156.1, 141.3, 138.5, 130.1, 125.2, 122.9, 109.4, 77.9, 72.9, 71.7, 67.2, 65.1, 56.2, 41.1, 39.6, 38.9, 38.6, 38.4 ppm. The reagent 9-iodo-9-BBN (1 M; 0.07 mL, 0.07 mmol) in hexanes was added to a solution of the alcohol (10 mg, 0.023 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C, and the resulting mixture was stirred for 10 h at room temperature. The reaction was then quenched with water (2 mL), and the aqueous layer was extracted with CH_2Cl_2 (2×2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/ethyl acetate=1:1) yielded **3** (8 mg, 80%) as a colorless solid. M.p.: 212 °C (decomp.); $[\alpha]_D^{23}$−48 (c=0.70, acetone); IR (film): $\tilde{\nu}$=3329, 2941, 2921, 1710, 1065, 1584, 1463, 1362, 1290, 1262, 1117, 1076, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.20 (t, J=7.9 Hz, 1H), 6.82 (d, J=8.3 Hz, 1H), 6.75 (d, J=7.5 Hz, 1H), 6.60–6.53 (m, 1H), 6.25 (d, J=14.5 Hz, 1H), 5.90 (s, 1H), 5.56–5.51 (m, 1H), 4.34–4.28 (m, 1H), 4.07–4.05 (m, 1H), 3.90–3.84 (m, 1H), 3.52 (dd, J=11, 14.3 Hz, 1H), 2.51–2.40 (m, 3H), 2.02–1.96 (ddd, J=4.7, 4.7, 12.9 Hz, 1H), 1.91–1.79 (m, 2H), 1.69–1.58 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.5, 153.2, 141.1, 138.7, 131.3, 122.7, 122.2, 115.5, 78.5, 73.4, 72.5, 66.5, 65.1, 41.2, 39.8, 39.4, 38.9, 37.5 ppm; HRMS: m/z calcd for $C_{18}H_{21}IO_5$: 445.0512 $[M+H]^+$; found: 445.0514.

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