Enantioselective Synthesis of the Tetracyclic Core of Platensimycin

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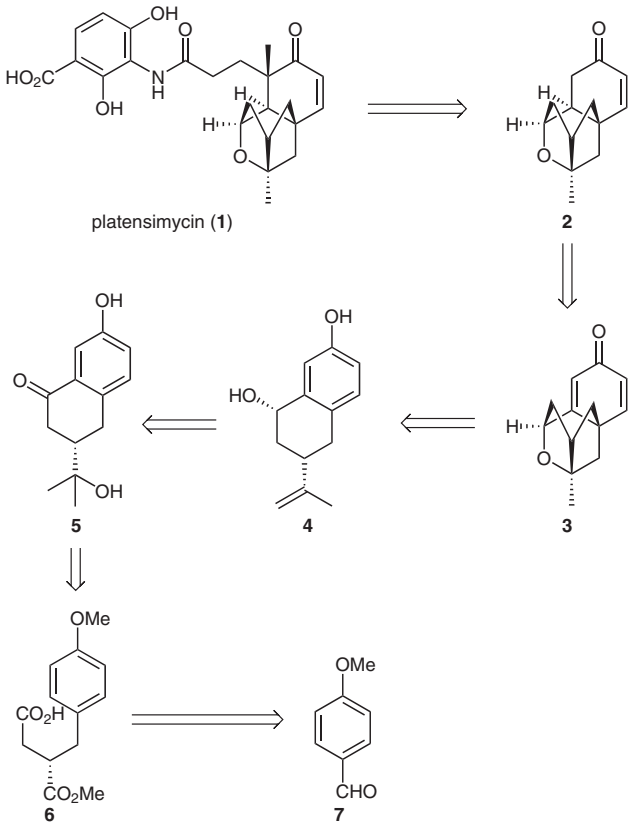
Abstract: A concise preparative method for the tetracyclic core of platensimycin in an optically active form was developed through a nine-step sequence from *p*-anisaldehyde without the use of protecting groups.

Key words: antibiotics, enantioselective hydrogenation, iodoetherification, formal synthesis

Platensimycin (**1**) has received much attention due to its biological activity and intriguing structural features. The Merck group discovered platensimycin in 2006 in a strain of *Streptococcus platensis* as a novel antibiotic compound against MRSA and VRE.[1,2] The cage-like tetracyclic core of platensimycin is of special interest as a synthetic target. Since the first total synthesis of platensimycin in racemic form was reported by Nicolaou et al.,[3] successful examples of the total synthesis and formal synthesis of platensimycin have been reported by several groups.[4,5] Almost all of them employed compound **2** as a key intermediate for the synthesis of **1**. Among them, Mulzer et al.[4g] and Corey et al.[4h] derived compound **2** from compound **3** through the reduction of both C=C bonds and re-oxidation for the construction of cyclohexenone moiety. During the effort for the diastereoselective reduction of C=C bond, Mulzer et al. employed Crabtree's catalyst to obtain the desired stereoisomer predominantly.[4g] Corey et al. obtained good diastereoselectivity during the reduction of double bond by employing a chiral catalyst for the hydrogenation reaction.[4h] For the synthesis of **3** in an optically active form, Corey et al. employed an enantioselective 1,4-addition of an isopropenyl group, followed by bromoetherification and intramolecular substitution for the construction of the tetracyclic core.[4h] Herein, we describe the formal synthesis of the optically active tetracyclic core **3** from *p*-anisaldehyde by using less expensive reagents in a stereoselective and protecting-group-free manner.

Our synthetic strategy is shown in Scheme 1. Compound **3**, which was previously reported by Mulzer et al.[4g] and Corey et al.,[4h] would be synthesized from **4** through iodoetherification and subsequent intramolecular substitution reaction. Compound **4** could be prepared by the site-selective β-elimination of the tertiary hydroxy group followed by the stereoselective reduction of the ketone moiety of compound **5**. Compound **5** would be constructed from compound **6** by intramolecular Friedel–Crafts acylation and the addition reaction of methyl groups to the ester moiety. Compound **6** could be easily obtained from *p*-anisaldehyde (**7**) through Stobbe condensation and following enantioselective reduction of the C=C bond.



Scheme 1 Synthetic plan for platensimycin

The synthesis of compound **10** is outlined in Scheme 2. Known compound **9**[6,7] was prepared from *p*-anisaldehyde (**7**) through Stobbe condensation, followed by enantioselective reduction of the C=C bond, and polyphosphoric acid-mediated intramolecular Friedel–Crafts acylation. Compound **6** was reported by Zhang et al. in an optically active form.[8] [Rh(TangPhos)(nbd)]SbF_6 was used as a catalyst for an enantioselective reduction of compound **8** affording compound **6** in 97% ee. An enantioselective reduction of compound **8** was also examined by using $Rh(cod)_2BF_4$ with (*R*,*R*)-Et-DuPhos, which gave **6** in 98% ee in quantitative yield. Masaguer et al. reported the use of TFA and TFAA for the intramolecular Friedel–Crafts acylation of compound **6**, and **9** was obtained in 50% yield.[6] We succeeded in improving the yield at this stage

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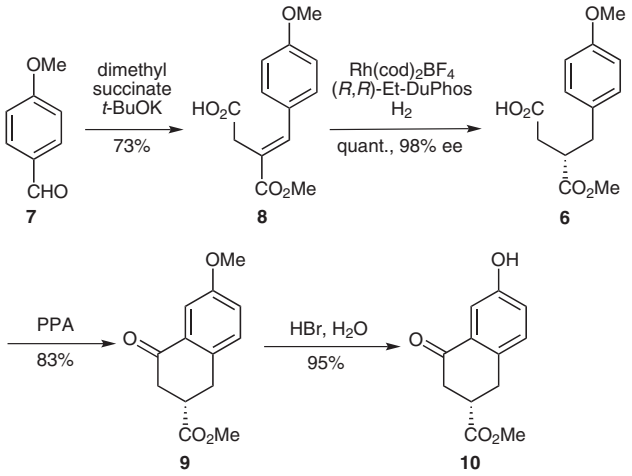
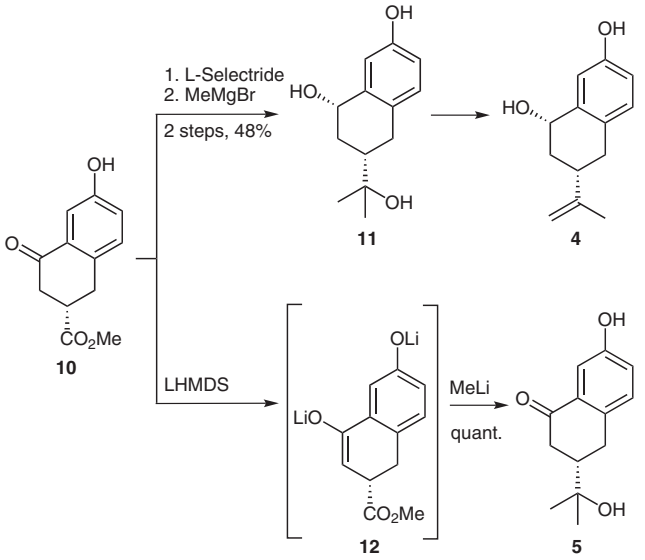
by employing polyphosphoric acid (83% yield). For the cleavage of the methyl ether on the aromatic ring, the presence of the ketone moiety conjugated on the aromatic ring is crucial. After the reduction of the ketone moiety, the cleavage of the methyl ether was unsuccessful. Therefore, the methyl ether was cleaved at this stage. Compound **9** was treated with aqueous HBr to give compound **10** in 95% yield.



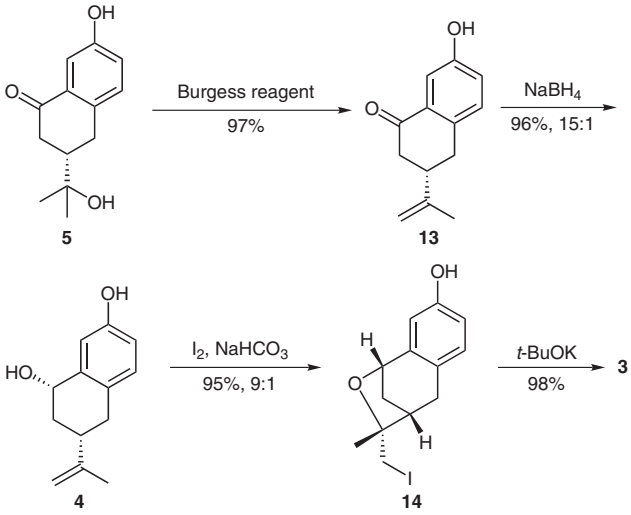
Scheme 2 Synthesis of compound **10**

For the synthesis of **4**, which is a precursor of the iodoetherification reaction, the ketone and methoxycarbonyl moieties of compound **10** must be converted into hydroxy and isopropenyl groups, respectively. As shown in Scheme 3, the reduction of the ketone moiety and the addition of the dimethyl groups to the methoxycarbonyl moiety of compound **10** proceeded smoothly to give compound **11**. However, the selective elimination of the tertiary hydroxy group of **11** to construct the isopropenyl group was unsuccessful. Therefore, the elimination of the tertiary hydroxy group of compound **5** was examined next. For the preparation of compound **5**, the protection of the ketone moiety of **10** was required. Thus, the ketone moiety of **10** was converted into enolate **12** in situ, and the addition of the methyl group was examined. Treatment of compound **10** with two equivalents of lithium bis(trimethylsilyl)amide (LHMDS) at –78 °C followed by the addition of methyllithium gave compound **5** in quantitative yield without significant racemization (96% ee). If required, compound **5** can be recrystallized to furnish almost enantiomerically pure **5** (99.5% ee) without significant loss of sample (>90% yield).

As shown in Scheme 4, the elimination of the tertiary hydroxy group of **5** for the construction of the isopropenyl group was achieved by the use of the Burgess reagent,[9] which can be easily prepared from chlorosulfonyl isocyanate, methanol, and triethylamine; and compound **13** was obtained in 97% yield. The reduction of the ketone moiety of **13** proceeded by employing sodium borohydride to give compound **4** in a highly diastereoselective manner (96% yield, diastereomeric ratio = 15:1). Iodoetherification of **4** afforded compound **14** in 95% yield (diastereomeric ratio = 9:1). The mechanism for the diastereoselectivity at this stage was proposed by Corey et al.[4h] for the bromoetherification of their substrate. Cyclization of **14** for the construction of the tetracyclic core **3** was achieved by treatment of **14** with potassium *tert*-butoxide in *tert*-butyl alcohol under refluxing conditions (98% yield). The spectral data and optical rotation value of compound **3** was identical to those reported in the literature.[4h]



Scheme 3 One-pot synthesis of compound **5**



Scheme 4 Synthesis of compound **3**

In conclusion, the formal synthesis of platensimycin (**1**) was realized. For the enantioselective synthesis of key intermediate **3**, nine steps were required from *p*-anisaldehyde and the total yield obtained was 46% (after removal of undesired diastereomer). In particular, a total 61% yield was attained from compound **8**, which was the Stobbe condensation adduct in the first step. The present route represents a stereoselective and atom-economical synthe-

sis for the tetracyclic core of platensimycin that employs less expensive reagents and avoids the use of protecting groups.

All reactions were carried out under an argon atmosphere. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AV-300 spectrometer and the chemical shifts are given in ppm using $CHCl_3$ (7.26 ppm) in $CDCl_3$ and CH_3OH (3.34 ppm) in CD_3OD for ^{1}H NMR and $CDCl_3$ (77.0 ppm) and CD_3OD (49.8 ppm) for ^{13}C NMR as an internal standard, respectively. IR spectra were taken with a Perkin-Elmer Paragon 1000 FT-IR and only noteworthy absorptions were listed. Mass spectra were measured on a Micromass LCT spectrometer.

(*E*)-3-(Methoxycarbonyl)-4-(4-methoxyphenyl)but-3-enoic Acid (8)

To a solution of *t*-BuOK (7.22 g, 51.5 mmol) in anhyd *t*-BuOH (40 mL) was added a solution of *p*-anisaldehyde (**7**; 5.84 g, 42.9 mmol) and dimethyl succinate (7.51 g, 6.7 mL, 51.5 mmol) in anhyd *t*-BuOH (15 mL) at 100 °C for 30 min under an argon atmosphere, and the resulting mixture was refluxed for 30 min. The reaction mixture was cooled to r.t., quenched with concd HCl (5 mL), and concentrated in vacuo. Ice-water was added to the residue and the mixture was extracted with Et_2O (2 × 200 mL). The combined organic extracts were washed with H_2O (80 mL), and extracted with sat. aq $NaHCO_3$ (2 × 100 mL). The aqueous layer was acidified with concd HCl, and the mixture was extracted with Et_2O (2 × 200 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc–AcOH, 200:100:3) to give the known compound **8**[6,7] as colorless crystals (7.78 g, 31.1 mmol, 73%); mp 117–118 °C (*n*-hexane–$CHCl_3$).

IR (KBr): 2938, 1706, 1639, 1607, 1511, 1436 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.62 (s, 2 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 6.94 (d, *J* = 8.5 Hz, 2 H), 7.35 (d, *J* = 8.5 Hz, 2 H), 7.87 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.6, 52.4, 55.3, 114.2, 122.9, 127.1, 131.0, 142.4, 160.4, 168.3, 177.1.

HRMS-ESI: *m*/*z* calcd for $C_{13}H_{14}O_5$ + Na (M + Na)$^+$: 273.0739; found: 273.0726.

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.54; H, 5.71.

(*S*)-3-(Methoxycarbonyl)-4-(4-methoxyphenyl)butanoic Acid (6)

Under an argon atmosphere, a mixture of $Rh(cod)_2BF_4$ (16.2 mg, 40.0 μmol) and (*R*,*R*)-Et-DuPhos (14.5 mg, 42.3 μmol) in CH_2Cl_2 (2 mL) was stirred at r.t. for 30 min. To the mixture was added compound **8** (1.00 g, 4.00 mmol) in one portion. The hydrogenation apparatus was purged three times with H_2 and filled with H_2 to 150 psi. After stirring for 24 h at r.t., the mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 1:1) to give the known compound **6**[8] as a colorless oil (1.01 g, 4.00 mmol, ~100%) with 98% ee (ee was determined after converting of **6** into methyl ester, and by using chiral column OD-H, *n*-hexane–*i*-PrOH, 95:5); $[\alpha]_D^{23}$ –33.9 (*c* 0.21, $CHCl_3$).

IR (film): 3235, 2954, 1732, 1713, 1613, 1514, 1440 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (dd, *J* = 4.7, 17.2 Hz, 1 H), 2.63–2.78 (m, 2 H), 2.92–3.13 (m, 2 H), 3.67 (s, 3 H), 3.77 (s, 3 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 7.06 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.6, 36.8, 42.9, 52.0, 55.2, 114.0, 129.9, 130.0, 158.5, 174.5, 177.4.

HRMS-ESI: *m*/*z* calcd for $C_{13}H_{16}O_5$ + Na (M + Na)$^+$: 275.0919; found: 275.0895.

(*S*)-Methyl (6-Methoxy-4-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)carboxylate (9)

A mixture of compound **6** (50 mg, 0.2 mmol) and polyphosphoric acid (600 mg) was stirred with a mechanical stirrer at 50 °C for 1 h. H_2O (5 mL) was added to the reaction mixture and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with aq $NaHCO_3$ (20 mL), H_2O (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 2:1) to give the known compound **9**[6,7] as colorless crystals (38.5 mg, 0.16 mmol, 83%) with 98% ee (ee was determined using chiral column OJ-H, *n*-hexane–*i*-PrOH, 97:3); $[\alpha]_D^{23}$ +47.7 (*c* 0.44, $CHCl_3$); mp 76–78 °C (*n*-hexane–$CHCl_3$).

IR (KBr): 2926, 1734, 1679, 1608, 1497, 1438 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.76–2.87 (m, 1 H), 2.87–2.98 (m, 1 H), 3.09–3.24 (m, 3 H), 3.72 (s, 3 H), 3.84 (s, 3 H), 7.09 (dd, *J* = 2.8, 8.4 Hz, 1 H), 7.19 (d, *J* = 8.4 Hz, 1 H), 7.51 (d, *J* = 2.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.2, 40.2, 40.5, 52.2, 55.4, 109.0, 122.2, 130.0, 132.6, 134.0, 158.6, 173.6, 195.8.

HRMS-ESI: *m*/*z* calcd for $C_{13}H_{15}O_4$ (M + H)$^+$: 235.0970; found: 235.0983.

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.79; H, 6.11.

(*S*)-Methyl (6-Hydroxy-4-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)carboxylate (10)

HBr (2.0 mL, 48% in H_2O) was added to compound **9** (100 mg, 0.43 mmol) at 90 °C. After stirring at 90 °C for 2 h, MeOH (2.0 mL) was added to the mixture. The reaction mixture was cooled to r.t. and H_2O (10 mL) was added to the mixture. MeOH was removed in vacuo and the residue was filtered and the crystals were washed with H_2O (10 mL). The crystals were dried under vacuum to give **10** (89.5 mg, 0.41 mmol, 95%); $[\alpha]_D^{23}$ +52.7 (*c* 1.0, DMSO); mp 76–78 °C (MeOH).

IR (KBr): 3186, 1720, 1654, 1618, 1579, 1497, 1429, 1356 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 2.81–2.88 (m, 2 H), 3.07–3.30 (m, 3 H), 3.70 (s, 3 H), 7.02 (dd, *J* = 2.7, 8.3 Hz, 1 H), 7.20 (d, *J* = 8.3 Hz, 1 H), 7.36 (d, *J* = 2.7 Hz, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 30.2, 39.4, 39.5, 50.6, 110.9, 121.1, 129.3, 131.9, 132.3, 155.7, 173.4, 196.4.

HRMS-ESI: *m*/*z* calcd for $C_{12}H_{12}O_4$ (M + H)$^+$: 221.0814; found: 221.0806.

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.53; H, 5.56.

(*S*)-3-(Dimethylhydroxymethyl)-7-hydroxy-1-tetralone (5)

To a solution of keto ester **10** (400 mg, 1.81 mmol) in anhyd THF (20 mL) was slowly added a solution of LHMDS (3.40 mL, 3.63 mmol, 1.07 M in hexane) at –78 °C under an argon atmosphere. After stirring at –78 °C for 30 min, a solution of MeLi (9.1 mL, 9.1 mmol, 1.0 M in Et_2O) was added to the mixture at the same temperature. The mixture was stirred at –78 °C for 30 min. The mixture was warmed to r.t. and aq 1 M HCl (20 mL) was added to the mixture. The resulting mixture was extracted with EtOAc (2 × 40 mL) and the combined organic extracts were washed with brine (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on sil-

ica gel (*n*-hexane–EtOAc, 1:2) to give **5** as colorless crystals (398.2 mg, 1.81 mmol, ~100%) with 96% ee (ee was determined using chiral column AS-H, *n*-hexane–*i*-PrOH, 90:10); $[\alpha]_D^{23}$ +27.5 (*c* 0.95, MeOH); mp 175–177 °C (*n*-hexane–EtOAc).

IR (KBr): 3448, 3234, 2978, 1664, 1616, 1572, 1498 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 1.28 (s, 3 H), 1.29 (s, 3 H), 2.13 (tdd, *J* = 3.6, 12.2, 13.6 Hz, 1 H), 2.43 (dd, *J* = 13.7, 16.4 Hz, 1 H), 2.69–2.87 (m, 2 H), 3.02 (td, *J* = 2.7, 15.6 Hz, 1 H), 7.01 (dd, *J* = 2.7, 8.3 Hz, 1 H), 7.21 (d, *J* = 8.3 Hz, 1 H), 7.34 (d, *J* = 2.7 Hz, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 24.7, 25.1, 29.4, 39.6, 46.0, 70.2, 110.7, 121.0 129.5, 132.0, 135.0, 155.3, 199.4.

HRMS-ESI: *m*/*z* calcd for $C_{13}H_{16}O_3$ + Na $(M + Na)^+$: 243.0997; found: 243.1015.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.69; H, 7.28.

(*S*)-7-Hydroxy-3-(1-methylethenyl)-1-tetralone (13)

To a solution of **5** (100 mg, 0.45 mmol) in anhyd THF (5.0 mL) was added Burgess reagent[9] (162.3 mg, 0.68 mmol) at r.t. under an argon atmosphere. After stirring for 2 h at r.t., H_2O (20 mL) was added to the mixture and the resulting mixture was extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 3:1) to give **13** as an amorphous powder (88.7 mg, 0.44 mmol, 97%); $[\alpha]_D^{23}$ +25.8 (*c* 5.60, $CHCl_3$).

IR (KBr): 3421, 2924, 1671, 1610, 1500, 1450 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.81 (s, 3 H), 2.55 (dd, *J* = 13.7, 17.4 Hz, 1 H), 2.72–3.04 (m, 4 H), 4.82 (s, 1 H), 4.85 (br s, 1 H), 7.03 (dd, *J* = 2.8, 8.3 Hz, 1 H), 7.17 (d, *J* = 8.3 Hz, 1 H), 7.52 (d, *J* = 2.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 34.1, 42.4, 43.9, 110.8, 112.6, 122.1, 130.3, 132.7, 135.9, 146.6, 155.0, 199.5.

HRMS-ESI: *m*/*z* calcd for $C_{13}H_{15}O_2$ $(M + H)^+$: 203.1072; found: 203.1084.

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.04; H, 6.90.

(1*S*,3*S*)-1,7-Dihydroxy-3-(1-methylethenyl)-1,2,3,4-tetrahydronaphthalene (4)

To a solution of **13** (172.0 mg, 0.85 mmol) in MeOH (8.5 mL) was slowly added solution of $NaBH_4$ (32.2 mg, 0.85 mmol) in MeOH (0.9 mL) at –10 °C under an argon atmosphere. After stirring for 1 h at –10 °C, the mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 1:1) to give diol **4** as an amorphous powder (167.4 mg, 0.82 mmol, 96% yield, diastereomeric ratio = 15:1); $[\alpha]_D^{23}$ +105.8 (*c* 0.65, EtOH).

IR (KBr): 3256, 2948, 1616, 1506, 1458 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 1.59 (dt, *J* = 11.0, 12.2 Hz, 1 H), 1.83 (s, 3 H), 2.25 (tdd, *J* = 2.1, 5.9, 12.0 Hz, 1 H), 2.40 (br dt, *J* = 4.2, 11.3 Hz, 1 H), 2.62 (dd, *J* = 11.7, 15.6 Hz, 1 H), 2.76 (ddd, *J* = 1.5, 4.9, 15.6 Hz, 1 H), 4.75 (dd, *J* = 5.9, 10.9 Hz, 1 H), 4.80 (br s, 1 H), 4.83 (br s, 1 H), 6.63 (dd, *J* = 2.4, 8.3 Hz, 1 H), 6.91 (d, *J* = 8.3 Hz, 1 H), 7.03 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 18.7, 33.6, 37.8, 40.2, 68.7, 107.6, 112.0, 113.5, 126.3, 128.4, 139.8, 148.3, 154.6.

HRMS-ESI: *m*/*z* calcd for $C_{13}H_{16}O_2$ + Na $(M + Na)^+$: 227.1048; found: 227.1058.

(1*S*,9*S*,10*R*)-4-Hydroxy-10-iodomethyl-10-methyl-11-oxatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene (14)

To a mixture of **4** (20 mg, 0.0979 mmol) and solid $NaHCO_3$ (82.3 mg, 0.979 mmol) in MeCN (1 mL) was added I_2 (49.7 mg, 0.196 mmol) at r.t. under an argon atmosphere in the dark. After stirring for 2 h at r.t., the mixture was treated with aq $NaHSO_3$ (5 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 2:1) to give **14** as an amorphous powder (30.7 mg, 0.0931 mmol, 95% yield, diastereomeric ratio = 9:1). Both diastereomers were separated by HPLC on silica gel (*n*-hexane–EtOAc, 2:1).

Major Isomer

$[\alpha]_D^{23}$ +140.8 (*c* 0.8, $CHCl_3$).

IR (KBr): 3370, 3078, 2921, 1611, 1508, 1450 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.56 (s, 3 H), 2.10 (d, *J* = 11.3 Hz, 1 H), 2.51–2.70 (m, 2 H), 3.01 (dd, *J* = 4.1, 17.5 Hz, 1 H), 3.13 (d, *J* = 9.8 Hz, 1 H), 3.21 (d, *J* = 17.5 Hz, 1 H), 3.30 (d, *J* = 9.8 Hz, 1 H), 4.80 (d, *J* = 5.1 Hz, 1 H), 6.60 (d, *J* = 2.6 Hz, 1 H), 6.75 (dd, *J* = 2.6, 8.2 Hz, 1 H), 6.93 (br s, 1 H), 7.00 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 28.0, 31.3, 35.3, 41.8, 78.5, 84.4, 114.3, 115.9, 125.2, 130.0, 140.6, 154.5.

HRMS-ESI: *m*/*z* calcd for $C_{13}H_{16}IO_2$ $(M + H)^+$: 331.0195; found: 331.0192.

Minor Isomer

IR (film): 3325, 2952, 1619, 1404, 1455 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 2.02 (d, *J* = 11.8 Hz, 1 H), 2.44 (td, *J* = 5.5, 11.8 Hz, 1 H), 2.82–3.11 (m, 3 H), 3.22 (d, *J* = 9.9 Hz, 1 H), 3.33 (d, *J* = 9.9 Hz, 1 H), 4.76 (d, *J* = 5.2 Hz, 1 H), 5.40 (br s, 1 H), 6.52 (d, *J* = 2.6 Hz, 1 H), 6.71 (dd, *J* = 2.6, 8.2 Hz, 1 H), 6.97 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.0, 23.6, 32.2, 34.7, 40.3, 78.4, 83.7, 114.1, 115.5, 125.7, 129.9, 140.7, 153.8.

HRMS-ESI: *m*/*z* calcd for $C_{13}H_{16}IO_2$ $(M + H)^+$: 331.0195; found: 331.0175.

(1*S*,7*S*,9*S*,10*S*)-10-Methyl-11-oxa-4-oxo-tetracyclo[7.2.1.1^{7,10}.0^{2,7}]trideca-2(3),5-diene (3)

To a stirred solution of **14** (50 mg, 0.151 mmol) in *t*-BuOH (1.5 mL) was added *t*-BuOK (85.0 mg, 0.757 mmol) at r.t. under an argon atmosphere. The resulting mixture was refluxed overnight. The reaction mixture was cooled to r.t., aq $NaHCO_3$ (10 mL) was added, and the resulting mixture was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 1:1) to give **3**[4h] as a colorless oil (30.0 mg, 0.148 mmol, 98%); $[\alpha]_D^{23}$ +32.5 (*c* 1.2, $CHCl_3$) {Lit.[4h] $[\alpha]_D^{23}$ +33.7 (*c* 1.25, $CHCl_3$)}.

IR (film): 2966, 1662, 1630, 1148 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.45–1.55 (m, 4 H), 1.76 (d, *J* = 11.3 Hz, 1 H), 1.92 (dd, *J* = 3.2, 11.2 Hz, 1 H), 1.98 (d, *J* = 11.2 Hz, 1 H), 2.11–2.27 (m, 2 H), 2.58 (t, *J* = 6.2 Hz, 1 H), 4.69 (d, *J* = 4.4 Hz, 1 H), 6.10 (d, *J* = 1.8 Hz, 1 H), 6.30 (dd, *J* = 1.8, 10.0 Hz, 1 H), 6.65 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 42.5, 44.4, 48.6, 49.9, 54.8, 80.0, 87.1, 121.8, 130.0, 150.9, 160.4, 187.0.

HRMS-ESI: *m*/*z* calcd for $C_{13}H_{15}O_2$ $(M + H)^+$: 203.1072; found: 203.1082.

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