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Three-component coupling approach toward the synthesis of a resorcylic acid lactone framework

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ABSTRACT

A resorcylic acid lactone (RAL) framework was constructed based on a three-component coupling approach. The key step was the intermolecular alkylation of a protected cyanohydrin with an aromatic scaffold, and the subsequent carbonylative esterification of the aryl iodide with an alcohol. This sequence allowed the rapid assembly of three components without extra protection/deprotection steps. This synthetic strategy enables the ketone at the 2′ position to be masked as a protected cyanohydrin during the ester formation, thus avoiding an undesired isocoumarin formation. This method should be widely applicable to the synthesis of various types of RAL frameworks.

1. Introduction

Resorcylic acid lactones (RALs) are polyketide natural products with a large macrocyclic ring fused to resorcylic acid (Fig. 1). RALs were discovered with the first isolation of radicicol (**1**) in 1953.[1] Although RALs did not attract much attention in the early years, recent discoveries of potent ATPase and kinase inhibitors amongst the RALs have revived interest in this family of natural products.[2–5] RALs have various functionalities, such as alkane, alkene, epoxide, and methyl ketone at the 1′ and 2′ positions (Fig. 1), and these functionalities do affect their target selectivities (see RALs **5** and **6** in Fig. 1).[2,6]

There have been numerous elegant synthetic reports related to RALs and their analogues.[2–21] In the early 1980s, we reported a zearalenone (**2**) analogue synthesis through palladium-catalyzed carbonylative esterification.[22–25] Although the carbonylative esterification required the activation of the sterically hindered *ortho*-disubstituted aryl iodide, the reaction proceeded well to give the desired benzoate in good yield. We also reported the construction of the macrolactone ring via intramolecular alkylation using a protected cyanohydrin.[24–26] In 2010, we reported a divergent, protection/deprotection-free, short synthetic route for the construction of RAL frameworks based on a three-component coupling approach.[27] The key step was a sequential palladium-catalyzed coupling reaction using an aromatic scaffold that had two reaction centers (Ar–I and Ar–Br) and a subsequent ring-closing metathesis (RCM) reaction.[28–30]

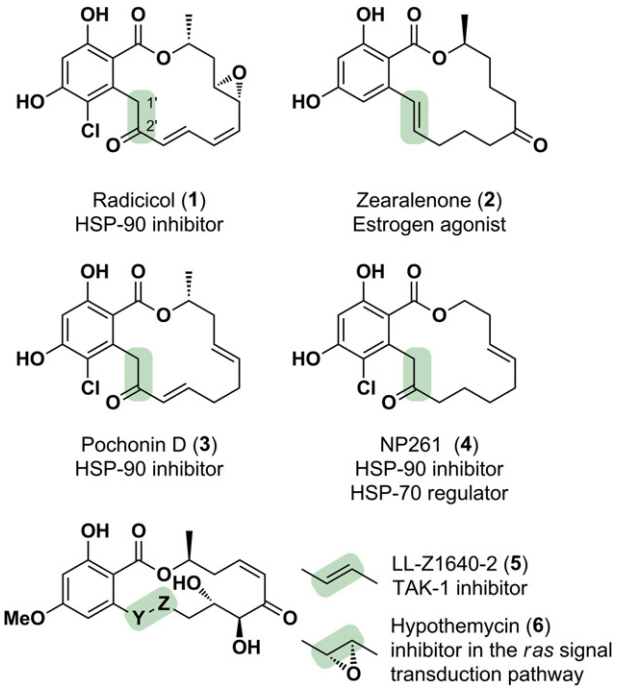

Fig. 1. Structures of naturally occurring RALs. Functionalities at the benzylic position are emphasized.

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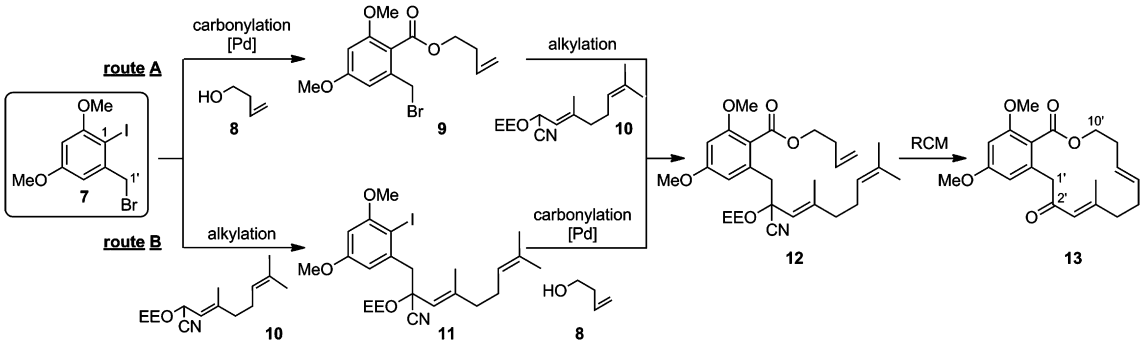


Scheme 1. Three-component coupling approach based on the aromatic scaffold **7**.

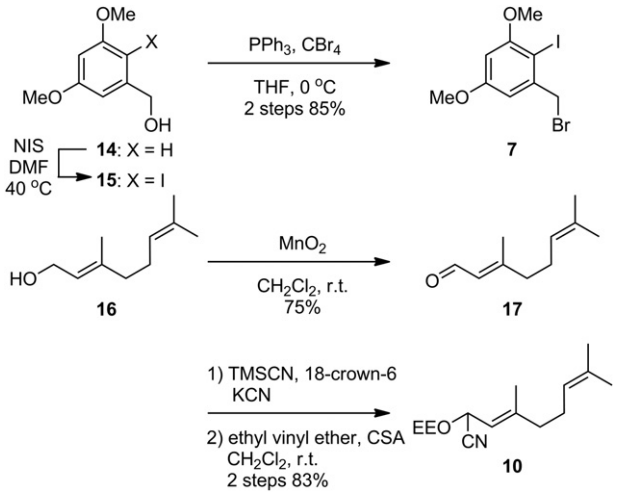
Herein, we wish to report the efficient synthesis of RAL analogue **13** with a methyl ketone functionality at its 1′ and 2′ positions based on a three-component coupling approach (Scheme 1). The key step was an alkylation/carbonylation sequence using an aromatic scaffold **7**, which had two reaction centers (Ar–I and $ArCH_2$–Br).

We planned to examine two synthetic routes toward the cyclization precursor **12**, i.e., routes A and B (Scheme 1). Both routes include the rapid assembly of three components, **7**, **8**, and **10**, without extra protection/deprotection steps. At the final stage, the macrocycle is formed under mild and neutral conditions by an RCM reaction. It is well known that the proton at the 1′ position in **13** is highly acidic and the ketone is readily enolised to yield an undesired isocoumarin.[26] Therefore, we decided to employ the building block **10**, in which the ketone at the 2′ position was masked as a protected cyanohydrin. We anticipated that the protected cyanohydrin would be readily converted into the corresponding ketone by treatment with a weak acid and a diluted base without forming the undesired isocoumarin.[26] The iodo-group at the 1 position would serve as a masked activated ester and the Ar–I bond could be activated by a palladium catalyst to directly form the desired ester.[22–25,31,32] In route A, the carbonylative esterification of the aromatic scaffold **7** with alcohol **8**, followed by intermolecular alkylation with the protected cyanohydrin **10** afford the desired coupling product **12**. In route B, the order of the carbonylation and the alkylation is switched. We speculated that the activation of the Ar–I bond in the aromatic scaffold **7** (route A) would be easier than the activation of the more sterically hindered Ar–I bond in **11** (route B). However, selective alkylation at the 1′ position to afford **11** without affecting the Ar–I bond (route B) seemed easier than selective carbonylation at the 1 position to afford **9** without affecting the $ArCH_2$–Br bond (route A). We examined both routes toward the synthesis of RAL analogue **13**.

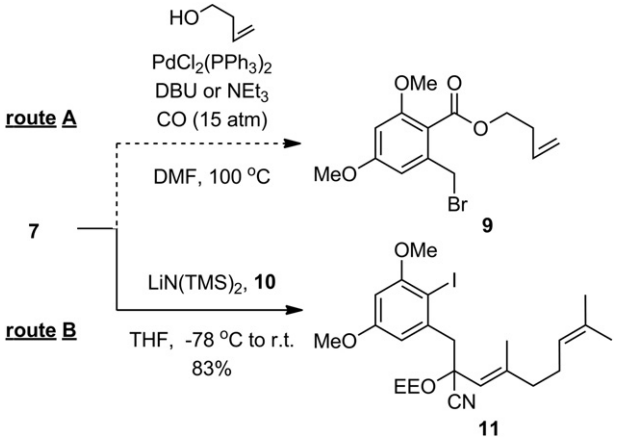
2. Results and discussion

Syntheses of the aromatic scaffold **7** and the protected cyanohydrin **10** are shown in Scheme 2. Iodination at the 1 position in commercially available, 3,5-dimethoxybenzyl alcohol (**14**) and the subsequent conversion of the benzyl alcohol to the corresponding benzyl bromide afforded the desired product **7** in high yield. The protected cyanohydrin **10** was readily prepared from geraniol (**16**) as shown in Scheme 2. The geraniol was oxidized to the corresponding citral (**17**), and the aldehyde was converted to the protected cyanohydrin **10** in two steps.

Initially, we examined the carbonylative esterification of **7** with 3-buten-1-ol (Scheme 3, route A). Although the aryl iodide **7** was consumed, a complex mixture was obtained and the desired ester



Scheme 2. Preparation of the pivotal aromatic scaffold **7** and the protected cyanohydrin **10**.



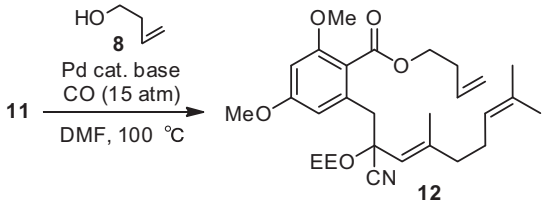
Scheme 3. Examination of synthetic routes A and B.

was not detected under the employed conditions [5 mol % $PdCl_2(PPh_3)_2$, DBU or NEt_3, CO (15 atm), DMF, 100 °C]. We concluded that the selective activation of the Ar–I bond in **7** without affecting the reactive $ArCH_2$–Br bond is difficult.[33]

Next, we examined route B (Scheme 3). The intermolecular alkylation of the protected cyanohydrin **10** with the aromatic scaffold **7** afforded the desired coupling product **11** in good yield.

The crucial palladium-catalyzed carbonylation was examined as shown in Table 1. The solution of the aryl iodide **11** and 3-buten-1-ol in DMF was vigorously stirred under a CO (15 atm) atmosphere at 100 °C. The combination of 5 mol % $Pd(Pt\text{-}Bu_3)_2$ and DABCO afforded a complex mixture accompanied by a trace amount of desired ester **12** (Table 1, entry 1). Better yields were observed by employing DBU (entries 2–4) and K_2CO_3 (entry 5) as the base. The combination of 5 mol % $PdCl_2(PPh_3)_2$ and DBU gave the best result (entry 4). The yield (61%) was satisfactory considering that the Ar–I bond of **11** was highly deactivated by the bulky and electron-donating *ortho*, *para*-trisubstituents.

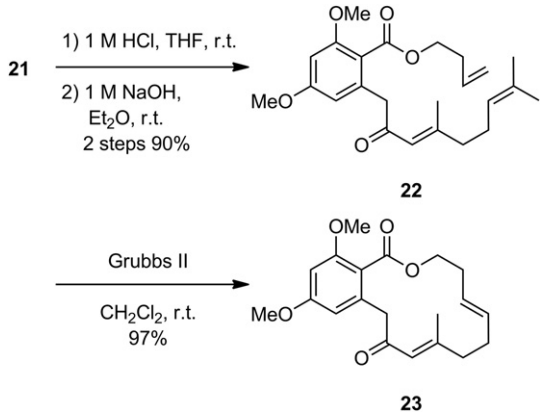
Table 1
Palladium-catalyzed carbonylative esterification



Entry	Pd cat.	Base	Yield[a] (%)
1	$Pd(Pt\text{-}Bu_3)_2$	DABCO	<10
2	$Pd(Pt\text{-}Bu_3)_2$	DBU	47
3	$Pd(OAc)_2$	DBU	24
4	$PdCl_2(PPh_3)_2$	DBU	61
5	$PdCl_2(PPh_3)_2$	K_2CO_3	40

[a] Isolated yield.

As expected, the conversion of the protected cyanohydrin **12** to the corresponding ketone **18** was successfully performed without generating the undesired isocoumarin. Finally, the macrolactone ring was formed via an RCM reaction using the Grubbs II[34] catalyst in excellent yield without affecting the methyl ketone functionality. Interestingly, the (*E*)-isomer was obtained as the sole product (Scheme 4).



Scheme 4. Total synthesis of RAL analogue **13**.

3. Conclusion

In summary, the synthesis of RAL analogue **13** was accomplished with a methyl ketone functionality at the 1′ and 2′ positions based on a three-component coupling approach. The RAL framework was rapidly assembled via an alkylation/carbonylation sequence without extra protection/deprotection steps. The crucial carbonylative esterification of highly deactivated aryl iodide **11** was achieved by using a combination of 5 mol % $PdCl_2(PPh_3)_2$ and DBU. As expected, the conversion of the protected cyanohydrin to the corresponding ketone was performed without generating the undesired isocoumarin. The desired compound **13** was synthesized via five steps from the pivotal aromatic scaffold in good yield (total 44% yield). This strategy should be widely applicable to the synthesis of various kinds of RAL analogues by changing the nucleophiles in the alkylation/carbonylation sequence.

4. Experimental section

4.1. General

NMR spectra were recorded on a JEOL Model EX-270 (270 MHz for ^1H, 67.8 MHz for ^{13}C) or a JEOL Model ECP-400 (400 MHz for ^1H, 100 MHz for ^{13}C) instrument in the indicated solvent. Chemical shifts are reported in units parts per million (ppm) relative to the signal for internal tetramethylsilane (0 ppm for ^1H) for solutions in $CDCl_3$. NMR spectral data are reported as follows: chloroform (7.26 ppm for ^1H) or chloroform-*d* (77.1 ppm for ^{13}C). Multiplicities are reported by the following abbreviations: s; singlet, d; doublet, t; triplet, q; quartet, m; multiplet, br; broad, *J*; coupling constants in Hertz. IR spectra were recorded on a Perkin–Elmer Spectrum One FT-IR spectrophotometer. Only the strongest and/or structurally important absorption is reported as the IR data in cm^{-1}. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) with UV light, visualized by *p*-anisaldehyde solution, ceric sulfate or 10% ethanolic phosphomolybdic acid. Merck silica gel 60 (0.063–0.200 mm) was used for column chromatography. ESI-TOF Mass spectra were measured with Waters LCT Premier™ XE. HRMS (ESI-TOF) were calibrated with leucine enkephalin (SIGMA) as an internal standard.

*4.1.1. 1-(Bromoethyl)-2-iodo-3,5-dimethoxybenzene (**7**).* To a solution of 3,5-dimethoxybenzyl alcohol (**14**) (4.30 g, 25.5 mmol) in DMF (50.0 mL) was added *N*-iodosuccinimide (6.90 g, 30.6 mmol) at 0 °C under Ar. After being stirred at 40 °C for 3 h, the mixture was poured into Et_2O and H_2O, and extracted with ethyl acetate. The extract was washed with 10% aqueous $Na_2S_2O_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was used for the next reaction without further purification.

To a solution of the residue in THF (132 mL) were added PPh_3 (6.36 g, 24.3 mmol) and CBr_4 (10.1 g, 30.6 mmol) at 0 °C under Ar. After being stirred at 0 °C for 3 h, the mixture was poured into Et_2O and H_2O, and extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel, and eluted with 5% ethyl acetate in hexane to afford 1-(bromoethyl)-2-iodo-3,5-dimethoxybenzene (**7**) (7.79 g, 21.8 mmol, 85%) as a white solid. Mp 126–128 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, J=2.9 Hz, 1H), 6.36 (d, J=2.9 Hz, 1H), 4.63 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 161.0, 159.2, 141.8, 107.0, 98.8, 81.5, 56.5, 55.6, 39.4; FT-IR (solid) 2940, 1586, 1471, 1322, 1200, 1084, 942, 824 cm^{-1}; HRMS (ESI-TOF); $[M+H]^+$ calcd for $C_9H_{11}O_2BrI$, 356.8987; found 356.8984.

*4.1.2. Protected cyanohydrin **10**.* To a solution of citral (**17**)[35] (1.30 g, 8.54 mmol) were added TMSCN (1.4 mL, 11.3 mmol) and a catalytic amount of DC-18-crown-6 KCN complex at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was diluted with THF and 1 M HCl was carefully added at 0 °C (caution: HCN is generated). After being stirred at the same temperature for 30 min, the reaction mixture was extracted with Et_2O. The extract was

washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was used for the next reaction without further purification.

To a solution of the crude cyanohydrin in CH_2Cl_2 (10.0 mL) were added ethyl vinyl ether (1.64 mL, 17.1 mmol) and CSA (132 mg, 0.568 mmol) at 0 °C under Ar. After being stirred at room temperature for 1 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel, and eluted with 5% ethyl acetate in hexane to afford the protected cyanohydrin **10** (1.78 g, 7.08 mmol, 83%) as a colorless oil (diastereomeric mixture).

*4.1.3. Aryl iodide **11**.* To a solution of the protected cyanohydrin **10** (98.9 mg, 0.393 mmol) in THF (5.00 mL) was added dropwise $LiN(TMS)_2$ (0.454 mL, 1.00 M in toluene, 0.454 mmol) at −78 °C under Ar. After being stirred at the same temperature for 30 min, a solution of 1-(bromoethyl)-2-iodo-3,5-dimethoxybenzene (**7**) (108 mg, 0.303 mmol) in THF (3.00 mL) was added to the reaction mixture at −78 °C. After being stirred at 0 °C for 30 min, the mixture was poured into Et_2O and 1 M HCl, and extracted with Et_2O. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel, and eluted with 25% Et_2O in hexane to afford the aryl iodide **11** (133 mg, 0.252 mmol, 83%) as a colorless oil (diastereomeric mixture).

*4.1.4. Ester **12**.* In a glass vessel, to a suspension of the aryl iodide **11** (283 mg, 0.535 mmol) and 3-butene-1-ol (**8**) (0.136 mL, 1.60 mmol) in DMF (3.00 mL) were added $PdCl_2(PPh_3)_2$ (18.7 mg, 26.6 μmol) and DBU (0.160 mL, 1.07 mmol) under Ar. The vessel was placed in an autoclave, which was purged with CO three times before application of pressure (15 atm). After it was stirred at 100 °C for 12 h, the reaction mixture was poured into Et_2O and saturated aqueous NH_4Cl, and extracted with Et_2O. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel, and eluted with 30% Et_2O in hexane to afford the ester **12** (163 mg, 0.326 mmol, 61%) as a colorless oil (diastereomeric mixture).

*4.1.5. Cyclization precursor **18**.* To a solution of the protected cyanohydrin **12** (44.0 mg, 88.1 μmol) in THF (2.00 mL) was added 1 M HCl (2.00 mL) at room temperature. After being stirred at the same temperature for 3 h, the mixture was diluted with Et_2O and extracted with Et_2O. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was used for the next reaction without further purification.

To a solution of the residue in Et_2O (2.00 mL) was added 1 M NaOH (2.00 mL) at 0 °C. After being stirred at room temperature for 3 h, the mixture was diluted with Et_2O and extracted with Et_2O. The extract was washed with saturated aqueous NH_4Cl (caution: HCN is generated) and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel, and eluted with 15% ethyl acetate in hexane to afford the cyclization precursor **18** (31.7 mg, 79.2 μmol) (31.7 mg, 79.2 μmol, 2 steps 90%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.38 (d, J=2.4 Hz, 1H), 6.32 (d, J=2.4 Hz, 1H), 6.07 (s, 1H), 5.84 (ddt, J=17.4, 10.1, 6.8 Hz, 1H), 5.13 (d, J=17.4 Hz, 1H), 5.08–5.00 (m, 2H), 4.31 (t, J=6.8 Hz, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.72 (s, 2H), 2.46 (dt, J=6.8, 6.3 Hz, 2H), 2.13–2.11 (m, 7H), 1.67 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 196.8, 167.6, 161.6, 159.9, 158.8, 135.9, 134.2, 132.4, 123.0, 122.3, 117.0, 116.6, 107.1, 97.6, 64.1, 55.9, 55.4, 49.2, 41.3, 33.0, 26.1, 25.6, 19.5, 17.6; FT-IR (neat) 2925, 1723, 1685, 1605, 1457, 1424, 1330, 1275, 1161, 1097, 1048 cm^{-1}; HRMS (ESI-TOF); $[M+H]^+$ calcd for $C_{24}H_{33}O_5$, 401.2328; found 401.2326.

*4.1.6. The RAL analogue **13**.* To a solution of the cyclization precursor **18** (47.6 mg, 0.119 mmol) in CH_2Cl_2 (24.0 mL) was added Grubbs II catalyst (10.0 mg, 0.0119 mmol) at room temperature under Ar. After being stirred at the same temperature for 3 h, the mixture was filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (20% in ethyl acetate in hexane) to afford the RAL analogue **13** (39.8 mg, 0.115 mmol, 97%) as a white solid. Mp 117–118 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.38 (s, 2H), 5.90 (s, 1H), 5.38 (dt, J=15.5, 6.8 Hz, 2H), 5.30 (ddd, J=15.5, 6.3, 5.8 Hz, 2H), 4.34 (t, J=5.3 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.56 (s, 2H), 2.41 (dt, J=5.8, 5.3 Hz, 2H), 2.17–2.08 (m, 7H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 197.2, 168.2, 161.4, 158.2, 157.6, 134.9, 131.8, 128.0, 123.9, 117.6, 105.7, 97.7, 64.2, 55.9, 55.4, 48.7, 39.7, 31.6, 29.4, 19.8; FT-IR (solid) 2948, 1720, 1675, 1587, 1453, 1381, 1264, 1198, 1069, 961, 635 cm^{-1}; HRMS (ESI-TOF); $[M+H]^+$ calcd for $C_{20}H_{25}O_5$, 345.1702; found 345.1704.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.05.023. These data include MOL files and InChIKeys of the most important compounds described in this article.

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32. We have reported the carbonylative esterification of *ortho*, *para*-trisubstituted aryl iodide with various secondary alcohols to synthesize RALs as shown in Refs. 23 and 27 (65–76% yield). The developed synthetic route should be applicable to the synthesis of RALs that have a methyl group at the 10′ position.
33. We also examined Pd-catalyzed carbonylation by using the aromatic scaffold, which has two reaction centers (Ar–I and $ArCH_2$–Cl). No desired product was obtained in this case. $ArCH_2$–Cl was activated under the employed carbonylation condition [5 mol % $Pd(OAc)_2$, PPh_3, NEt_3, DMF, CO (15 atm), 80 °C].
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