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Synthesis of arotinoid acid and temarotene using mixed (*Z*)-1,2-bis(organylchalcogene)-1-alkene as precursor

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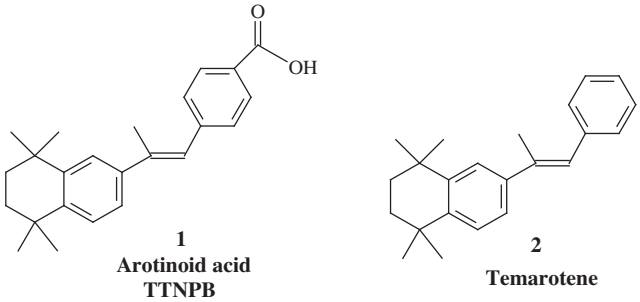
ABSTRACT

An efficient and novel total synthesis of the two bioactive retinoids temarotene and arotinoid acid (TTNPB) is described. The key steps in this process include the regio and stereoselective hydrotelluration of thioacetylene **9** and Te/Li transmetalation of mixed (Z)-1,2-bis(organylchalcogene)-1-alkene (Z)-**3**. The subsequent reaction involving the β-phenylthio vinyl lithiated intermediate **10** with dimethyl sulfate gave the (E)-vinyl sulfide **11**. The Ni^{+2} cross-coupling of **11** with the corresponding phenylzinc bromide and *p*-oxazoline phenylzinc bromide **12** afforded the respective temarotene **2** and retinoid-oxazoline substituted **13**. Finally, compound **13** was deprotected with HCl to furnish arotinoid acid (TTNPB) **1**.

Naturally occurring vitamin A-like compounds such as all-*trans*-retinoic acid (atRA)[1,2] are responsible for regulating growth and differentiation in the cell, and many of them have shown promising anticancer effects.[3–7] However, monocutaneous irritation, hyperlipidemia, bone toxicity, impaired night vision, and teratogenicity, have been observed as side effects after the use of these substances in therapy.[8] The analogues of atRA include the arotinoid acid 4-[(1***E***)-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-1-propen-1-yl] benzoic acid **1** (TTNPB)[9] which is a potent synthetic retinoid that shows a similar affinity as atRA, binding to all three nuclear retinoic-acid receptors (RARs).[10]

Bioassays in vivo and in culture showed that TTNPB is more potent than atRA, mainly because of its higher molecular stability.[11] The effects of TTNPB, which include control of epidermal keratinocytes[12] and murine teratocarcinoma cells[13] and antiproliferative effects on Kaposís sarcoma,[14] breast cancer,[15] cervical carcinoma,[16] and leukemia cells[17] have been known for some time. Furthermore, TTNPB proved to be 100 times more effective than atRA in inhibiting the growth of breast cancer cells.[18] However, TTNPB is more teratogenic than atRA, which limits its use as a chemotherapeutic agent in humans.[19] Thus, synthetic methodologies to prepare less toxic retinoid derivatives than TTNPB have been described. In this way, the [(1***E***)-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)]-1-phenyl-1-propene, known as temarotene[20] **2**, has long been used for chemoprevention of cancer[21] and has shown no important side effects such as hypervitaminosis A and teratogenicity. The lack of side effects is believed to be a consequence of the absence of the polar carboxyl group[22] as shown in Figure 1.

Srebnik and co-workers described the stereospecific synthesis of temarotene using the metal catalyzed cross-coupling reactions



1
Arotinoid acid
TTNPB

2
Temarotene

Figure 1. Chemical structure of retinoid products.

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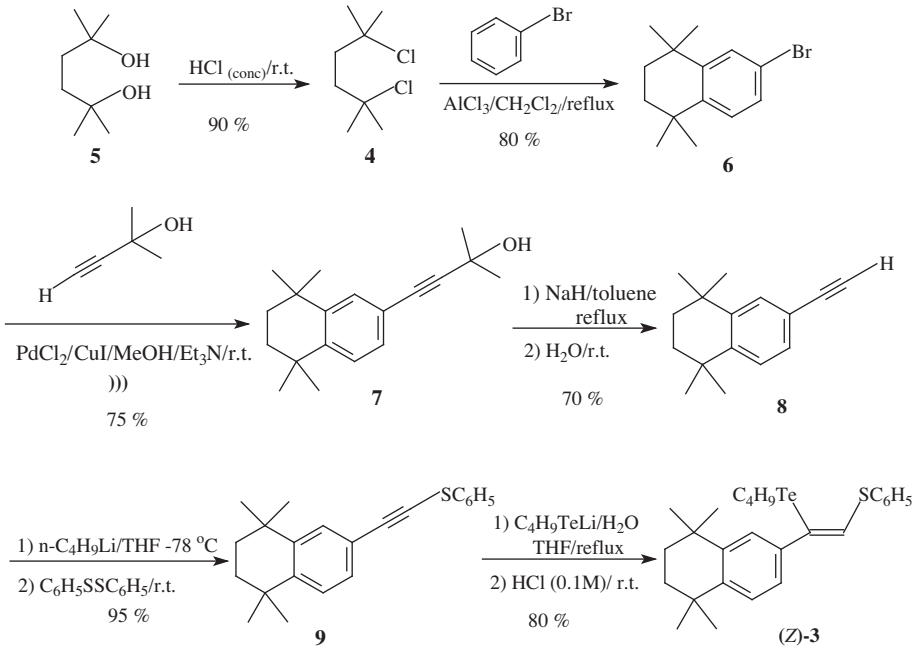
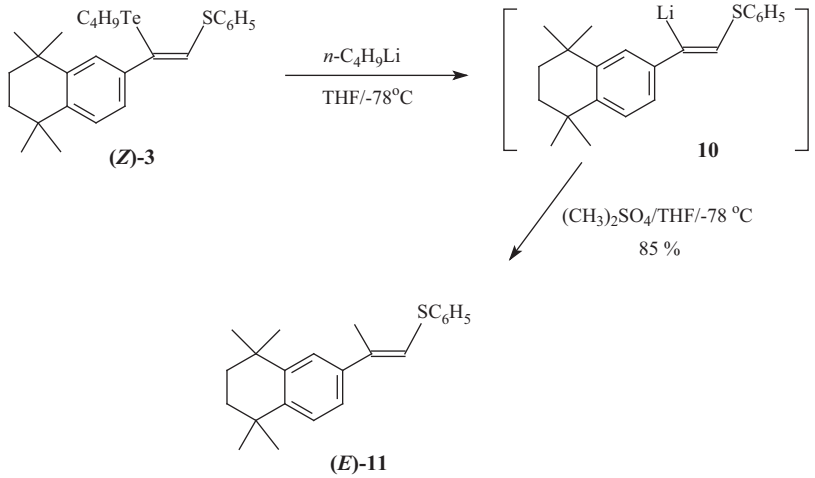


Scheme 1. Synthesis of fragment **3**.



Scheme 2. Synthesis of fragment **11**.

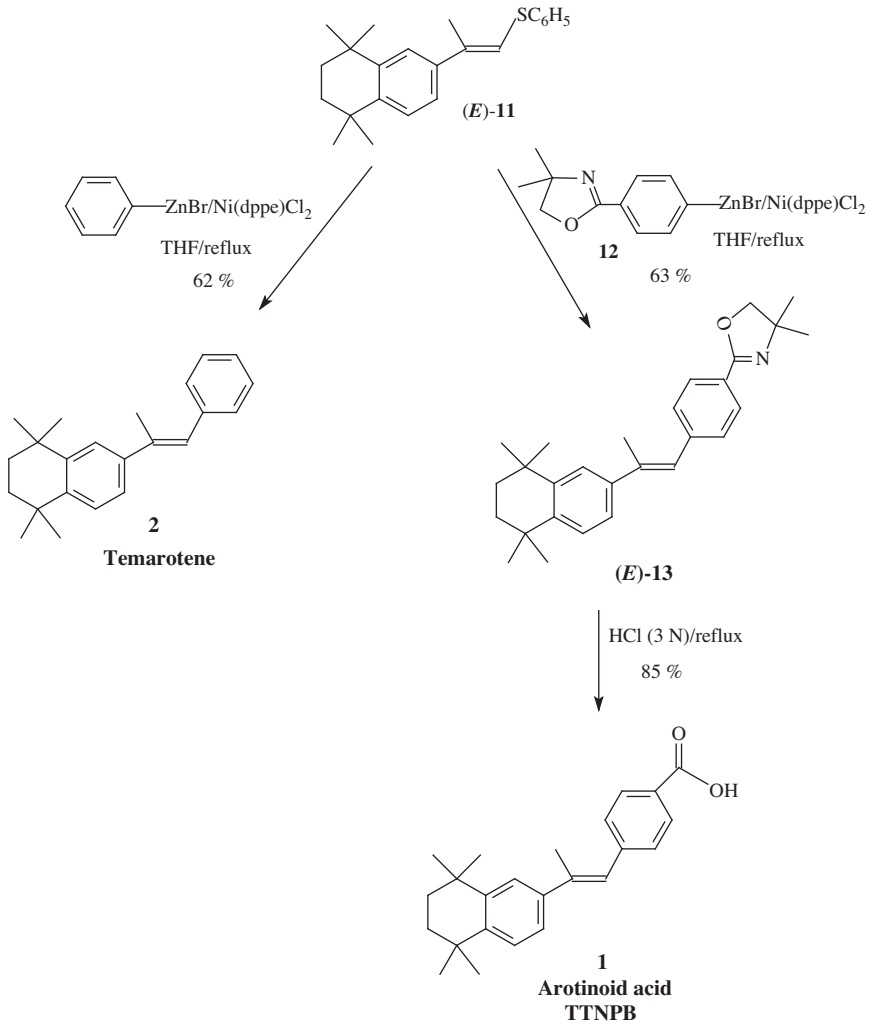
of *gem*-borazirconocene-1-alkenes.[23] However, the 1,1-dihetero bismetallic intermediate was generated by the hydrozirconation of 1-alkynylboranate with the expensive and air-sensitive $Cp_2Zr(H)Cl$ (Schwarts reagent).

More recently, Dame and co-workers described the 4-hydroxybenzyl structural modifications in TTNPB with *N*-(4-hydroxyphenyl) amido (4HPTTNPB) and 4-hydroxybenzyl (4-HBTTNB), investigated their high potential to induce apoptosis in breast cancer cells and demonstrated their low toxicity.[24]

Normally, TTNPB and analogues used in bioassay studies are synthesized upon Horner-Emmons olefination of aryl ketones using the anion diethyl(4-carboethoxybenzyl) phosphonate.[25] However, this method can lead to a diasteroisomeric mixture[25,26] of (***Z***) and (***E***)-TTNPB-type, and the use of phosphorus reagents has been avoided recently due to their high toxicity and generation of hazardous residues, and the tedious procedures involved in product purification, which limits the use of this protocol.[27]

Considering the interesting biological activities of the retinoids TTNPB and temarotene, and the need to apply these molecules as a prototype to construct new anticancer drugs, we describe herein a novel and straightforward total synthesis of these two (***E***)-retinoids with total regio and stereochemical control, by modifications of procedures described in the literature.[25] The key intermediate for both syntheses is (***Z***)-1-phenylthio-2-butyltelluro-2-[5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl] ethene **3** which was prepared as outlined in Scheme 1.

Thus, the solid 2,5-dichloro-2,5-dimethyl-hexane **4** was obtained in 90% yield by the addition of concentrated HCl to a solution containing 2,5-dimethyl-2,5-hexanediol **5**.[25b] Friedel-Crafts alkylation[28] of bromobenzene in the presence of $AlCl_3$ with dichloride compound **4** led to the bromo substituted tetralin **6**. Applying a Sonogashira-type cross-coupling reaction protocol recently developed by us[29] between **6** and 1,1-dimethyl-3-propyn-1-ol employing a system containing $PdCl_2/CuI/Et_3N$ in methanol under sonication, afforded the disubstituted bicyclic alkyne **7** (75% yield). The retro-Favorskii conditions[30] were utilized by deprotection of the terminal triple bond of **7** using NaH/toluene under reflux to give the terminal bicyclic alkyne **8** in 70% yield,



Scheme 3. Synthesis of temarotene and arotinoid acid (TTNPB).[32]

which was subsequently transformed into the corresponding thioacetylene **9** in 95% yield by the reaction with *n*-C_4H_9Li/THF followed by the addition of phenyl disulfide. Finally, performing the hydrotelluration[31,32] of **9** with C_4H_9TeLi/H_2O the (***Z***)-1-phenylthio-2-butyltelluro-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl) ethene **3** was achieved in 80% yield.

The next step in the synthesis of the desired compounds involved the selective Te/Li transmetalation of the key compound **3** with *n*-C_4H_9Li to produce the lithiated β-organylthio vinyl as recently described by our group.[31] As far as we know this is the first time that this transformation has been applied in the total synthesis of bioactive molecules.

Therefore, the reaction of (***Z***)-1-phenylthio-2-butyltelluro-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl) ethene **3** with *n*-C_4H_9Li at −78 °C produced in situ the β-phenylthio vinyl lithiated intermediate **10**, which was reacted with dimethyl sulfate to give the trisubstituted vinyl sulfide **11** in 85% yield (Scheme 2).[32]

So, the Ni^{+2} cross-coupling reaction of alkenyl sulfide **11** with the commercially available phenylzinc bromide or 2-(4-bromophenyl zinc)-4,4-dimethyl-2-oxazoline **12** [prepared separately by the addition of dry $ZnBr_2$ (1.0 equiv) at 0 °C to a solution of the 2-(4-bromophenyl magnesium)-4,4-dimethyl oxazoline[33] (1.0 equiv) in THF] using the inexpensive catalyst Ni(dppe)Cl_2, furnished respectively, the temarotene **2** in 62% yield and the oxazoline intermediate **13**, in 63% yield. Finally, the compound **13** was converted into arotinoid acid (TTNPB) in 85% yield by the hydrolysis of the oxazoline moiety using HCl (3 N) under reflux (Scheme 3).

In conclusion, we describe herein a novel and efficient total synthesis of the two important bioactive retinoids, temarotene, and arotinoid acid (TTNPB), using a selective stereocontrolled Te/Li transmetalation of the mixed (***Z***)-1,2-(organylchalcogenide)-1-alkene followed by Ni^{+2} catalyzed cross-coupling reaction between a vinyl sulfide with organozinc reagent as the key steps. Moreover, we describe for the first time the synthetic application of the β-organylthio vinyl lithiated intermediates type **10**, toward the total synthesis of bioactive molecules.

Further studies concerning the use of mixed (***Z***)-1,2-(organylchalcogenide)-1-alkenes to make interesting bioactive molecules such as sex pheromones and other anticancer synthetic retinoids such as bexarotene are in progress in our laboratory.

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32. *Experimental procedures for the synthesis of selected compounds*: *(Z)-1-Phenylthio-2-butyltelluro-2-[5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl]-ethene (**3**)*: To a two-neck flask under nitrogen atmosphere and magnetic stirring containing elemental tellurium (0.19 g, 1.5 mmol) in THF (6.0 mL) at 0 °C, *n*-butyllithium (1.5 mmol, 1.5 mL, 1.0 M in hexanes) was added dropwise. The mixture was stirred for 10 min at room temperature. Next, water (4.0 mL) followed by a solution of 1-thiophenyl-2-[5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl] ethyne **9** (0.48 g 1.5 mmol) in THF (5.0 mL) was transferred via syringe and the reaction mixture refluxed for 2.0 h. After cooling, the mixture was diluted with ethyl acetate (100 mL) and washed with brine (3 × 50 mL). The organic phase was dried under anhydrous $MgSO_4$. After filtration, the solvent was removed under vacuum and the crude product was purified by flash chromatography in silica gel (230–400 mesh) using hexane as mobile phase, furnishing the pure compound (Z)-**3** as yellow oil in 80% yield (0.40 g). IR (neat): 3011, 2923, 1847, 1755, 1490, 1458, 920 cm^{-1}; ^1H NMR (400 MHz, δ in $CDCl_3$) 7.43 (d, J = 7.5 Hz, 1H), 7.21–7.43 (m, 6H), 7.20 (d, J = 7.5 Hz, 1H), 6.83 (s, 1H), 2.51 (t, J = 7.5 Hz, 2H), 1.81 (s, 4H), 1.60 (quint, J = 7.5 Hz, 2H), 1.27 (s, 6H), 1.24 (s, 6H), 1.23 (sext, J = 7.5 Hz, 2H), 0.73 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz) 144.3, 144.2, 139.4, 135.8, 131.7, 129.5, 129.4, 129.1, 129.0, 126.9, 126.7, 126.4, 125.3, 122.2, 35.0, 34.9, 34.2, 34.1, 34.0, 31.8, 31.7, 25.0, 13.2, 8.8; HRMS (70 eV) required for $C_{26}H_{34}TeS$ (M^+) 508.1443, observed 508.1456.

*(E)-1-Phenylthio-2-[5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2 naphthalenyl]-1-propene (**11**)*: To a two-neck flask under nitrogen atmosphere and magnetic stirring bar containing a solution of (***Z***)-1-phenylthio-2-butyltelluro-2-[5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl]-ethene (**3**) (0.75 g, 1.5 mmol) in THF (5.0 mL) at −78 °C, *n*-butyllithium (1.5 mL, 1.5 mmol, 1.0 M in hexanes) was transferred via syringe and the reaction was stirred for 10 min. Next, dimethyl sulfate (0.20 mL, 2.0 mmol) was added and the mixture was stirred for additional 30 min. The reaction mixture was left to reach 25 °C, diluted with ethyl acetate (100 mL), and washed with brine (4 × 50 mL). The organic phase was dried under anhydrous $MgSO_4$. After filtration, the solvent was removed under vacuum and the crude product purified by flash chromatography in silica gel (230–400 mesh) using hexane as mobile phase to give the pure compound (E)-**11** as yellow oil in 85% yield (0.28 g). IR (neat): 2925, 1850, 1755, 1494, 1458, 920, 689 cm^{-1} ^1H NMR (400 MHz, δ in $CDCl_3$) 7.12–7.41 (m, 8H), 6.55 (s, 1H), 2.25 (s, 3H), 1.67 (s, 4H), 1.27 (s, 6H), 1.24 (s, 6H); ^{13}C NMR (75 MHz) 144.2, 144.1, 138.8, 138.4, 136.5, 128.9, 128.7, 126.5, 126.1, 123.4, 122.8, 119.6, 35.1, 34.9, 34.2, 34.0, 31.8, 31.5; GC/MS *m*/*z* required for $C_{23}H_{28}S$ (M^+) 336.5, observed 336.3.

*4-[(1E)-2-(5,5,8,8-tetramethyl-5,6,7,8 tetrahydro-2-naphthalenyl)]-1-phenyl-1-propene (**2**) (Temarotene)*: To a two-neck flask under nitrogen atmosphere and magnetic stirring bar containing a solution of (***E***)-1-Phenylthio-2-[5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2 naphthalenyl]-1-propene (**11**) (0.34 g, 1.0 mmol) in THF (8 mL) and $NiCl_2$(dppe) (0.026 g, 0.05 mmol) was added dropwise via syringe the C_6H_5ZnBr (4 mL, 2 mmol, 0.5 M in THF) and the mixture was stirred for 2.5 h under reflux. The reaction mixture was left to reach 25 °C, diluted with ethyl acetate (100 mL) and washed with brine (5 × 50 mL). The organic phase was dried under anhydrous $MgSO_4$. After filtration, the solvent was removed under vacuum and the crude product purified by flash chromatography in silica gel (230–400 mesh) using hexane as mobile phase to give the pure temarotene **2** as yellow oil in 55% yield (0.16 g). IR (neat) 2925, 1607, 1458, 922 cm^{-1}; ^1H NMR (400 MHz, δ in $CDCl_3$) 7.43 (d, J = 7.5 Hz, 1H), 7.33–7.35 (m, 4H), 7.29 (d, J = 7.5 Hz, 2H), 7.24 (m, 1H), 6.78 (s, 1H), 2.25 (s, 3H), 1.69 (s, 4H), 1.31 (s, 6H), 1.27 (s, 6H); ^{13}C NMR (75 MHz) 144.8, 144.1, 141.0, 138.6, 137.6, 129.1, 128.1, 127.0, 126.7, 126.4, 124.1, 123.5, 35.2, 34.1, 40.1, 31.9, 17.4; HRMS (70 eV) required for $C_{23}H_{28}$ (M^+) 304.2191, observed 304.2182.

*2-[4-(1E)-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-1-propen-1yl]phenyl-4,4-dimethyl-2-oxazoline (**13**)*: To a two-neck flask under nitrogen atmosphere and magnetic stirring bar containing a solution of (***E***)-1-phenylthio-2-[5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl]-1-propene **11** (0.34 g, 1.0 mmol) in THF (8.0 mL) and Ni(dppe)Cl_2 (0.026 g, 0.05 mmol) was added dropwise via syringe the 2-(4-bromophenyl zinc)-4,4-dimethyl-2-oxazoline **12** (2.0 mmol) [prepared separately by addition of dry $ZnBr_2$ (0.45 g, 2.0 mmol) to a solution of 2-(4-bromophenyl magnesium)-4,4-dimethyl oxazoline[33] (2.0 mmol) in THF (4.0 mL) at 0 °C and the mixture was stirred for 30 min] and the reaction stirred for 5 h under reflux. After cooling the mixture was diluted with ethyl acetate (100 mL) and washed with brine (5 × 50 mL). The organic phase was dried under anhydrous $MgSO_4$. After filtration, the solvent was removed under vacuum and the crude product purified by flash chromatography in silica gel (230–400 mesh) and hexane/ethyl acetate (9:1 v/v) as mobile phase to give the pure compound (E)-**13** in 63% (0.25 g). IR (neat) 2923, 1847, 1635, 1610, 1417, 920 cm^{-1}; ^1H NMR (400 MHz, δ in $CDCl_3$) 7.95 (d, J = 7.5 Hz, 2H), 7.52 (d, J = 7.5 Hz, 2H), 7.50 (s, 1H), 7.16 (s, 1H), 7.10 (s, 1H), 6.75 (s, 1H), 4.10 (s, 1H), 1.95 (s, 3H), 1.71 (s, 4H), 1.38 (s, 6H), 1.30 (s, 6H), 1.25 (s, 6H); ^{13}C NMR (75 MHz) 162.0, 149.2, 144.2, 143.2, 138.1, 132.7, 128.0, 126.8, 116.2, 79.0, 67.5, 35.1, 33.9, 31.9, 28.4, 19.9; Anal. Calcd for $C_{28}H_{35}NO$: C, 76.19; H, 8.73, Found C, 76.34; H, 8.90.

*4-[(1E)-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-1-propen-1yl]benzoic acid (**1**) (TTNPB)*: A solution containing (E)-**13**, (2.0 g, 5.0 mol) and hydrochloric acid (65 mL, 3 N) was refluxed for 3 h. Next, the reaction was cooled to 0 °C when a white precipitate formed. After filtration, the white crystals were washed with water (2 × 30 mL) and the solid crude product was recrystallized from acetic acid, furnishing the pure TTNPB **1** in 85% yield (0.31 g). mp 240–24 °C (lit. mp 239–240 °C)[24]; UV (DMSO) λ_{max} 312 nm (lit. λ_{max} 309 nm);[24] IR (Nujol) 1680, 1604, 1567, 795 cm^{-1}; ^1H NMR (400 MHz, δ in $CDCl_3$) 7.95 (d, J = 7.5 Hz, 2H), 7.52 (d, J = 7.5 Hz, 2H), 7.50 (s, 1H), 7.31 (s, 2H), 6.89 (s, 1H), 2.25 (s, 3H), 1.65 (s, 4H), 1.28 (s, 6H), 1.24 (s, 6H); ^{13}C NMR (75 MHz) 167.7, 144.8, 144.5, 142.9, 140.7, 139.6, 129.7, 129.6, 129.2, 126.9, 126.1, 124.2, 123.9, 35.2, 35.0, 34.5, 34.3, 32.1, 32.0, 17.9; Anal. Calcd for $C_{24}H_{28}O_2$: C, 82.74; H, 8.45, Found C, 83.02; H, 8.78.
33. The magnesium reagent 2-(4-bromophenyl magnesium)-4,4-dimethyl xazoline was generated in situ as described by Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787.