

J Org Chem. Author manuscript; available in PMC 2008 August 31.

Published in final edited form as:

J Org Chem. 2007 August 31; 72(18): 6885–6890. doi:10.1021/jo071156l.

Welwistatin Support Studies: Expansion and Limitation of Aryllead(IV) Coupling Reactions

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Abstract

$$\begin{array}{c|c}
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 & ArPb(OAc)_3 \\
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 & FWG \\
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 & ArPb(OAc)_3 \\
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 & FR_1 \\
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 & OPG \\
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Recent support studies on the total synthesis of the welwitstatin system are described. The target step involves lead-mediated arylation of sterically demanding aryl groups and carbon acid coupling partners in order to establish the highly congested tetracyclic core structure. Type 7 β -ketoesters and β -ketonitriles were successfully arylated with a variety of *ortho*- and *meta*-subsituted aryllead compounds generated by a halogen-boron-lead exchange sequence. The enolates of compounds 15, 19 and 25, each bearing all-carbon quaternary centers adjacent to the arylation site, failed to couple.

Introduction

Guided by biological activity data, Moore and coworkers described the isolation and structure elucidation of the welwitindolinones, a class of structurally distinct blue-green algae-derived alkaloids. Representative members of this class of compounds include welwitindolinone C isothiocyanate (welwistatin, 1), the *N*-methyl analog 2 and welwitindolinone A isonitrile (3). While the original interest in 1 and 2 was focused on the ability of these alkaloids to reverse P-glycoprotein-mediated multiple drug resistance (MDR), additional studies provided strong evidence for innate cytotoxicity at the nanogram level. 2

Interest in the total synthesis of welwitindolinones began slowly, with only our initial studies and the substantive efforts of Wood and coworkers published in the 20^{th} century. Synthetic efforts have increased substantially in the new millennium, with contributions from groups headed by Zard, Mayendaño, Avendaño, Rawal, Simpkins, Funk 10 and Shea. Notable among these achievements is the advanced intermediate produced by Greshock and Funk, which possesses both fully substituted centers at C11 and C12. In addition, the total synthesis of (+)-3 by Baran 12 and (±)-3 by Wood 13 have been communicated recently.

Our most recent published work described the synthesis of indole **4** and the corresponding *N*-methyloxindole **5**, prepared by the highly stereoselective formation of the C4-C11 bond (welwistatin numbering) via an aryllead(IV) coupling reaction. ¹⁴ Herein we disclose more recent efforts toward the welwistatin system, including 1) expansion of the scope of lead-mediated arylation to include a wider array of aryl substrates; 2) investigation of the lead coupling reaction on substrates, including enantiomerically pure substrates, already substituted at C12, so as to accomplish the challenging task of establishing welwistatin's contiguous quaternary centers. ¹⁵

Results and Discussion

The key limitation in incorporating a variety of aryl synthetic handles via lead arylation is the occasional difficulty in obtaining the lead reagents themselves. Lead reagents can generally be made in one of two ways: direct plumbation (which is limited to very simple systems) or, more commonly, metal-lead exchange reactions. ¹⁶ Standard protocol begins with an aryl halide, which undergoes sequential halogen-tin and tin-lead exchanges. While this sequence is generally quite reliable, we found it to fail in a number of the aryl substrates we envisioned to be potential oxindole precursors. Initially, it appeared that sterics played a role in limiting this exchange, as there were difficulties obtaining a number of *o*-alkylated lead reagents. However, additional troubles in generating both the *m*-nitro and the *m*-bromo aryllead(IV) reagents forced us to consider the importance of electronic interactions in the tin-lead exchange as well. Hence, we turned to boron-lead exchange as a method of generating our aryllead coupling partners.

In 1990, Morgan and Pinhey reported the generation of aryllead triacetates from the reaction of arylboronic acids and lead tetraacetate, 17 and Moloney has employed this technology extensively. 18 Several boronic acids of interest (**6a-c**) are commercially available; others, such as **6d**, can be synthesized easily from the corresponding aryl bromides via the methods of Li, et al. 19 (Scheme 1, eq 1). The lead reagent is then generated by treatment with lead (IV) acetate and a catalytic amount of mercury trifluoroacetate, followed by addition of the carbon acid coupling partner. The preparation of carbon acids **7a** and **7b** has already been described; 20 preparation of the –OTBDPS compound **7c** proceeds in like manner to **7b** (eq 2); namely, zinc enolate formation of **8**, 21 condensation with acetone/ dehydration (**9**), and enolate formation/ dimethyl carbonate treatment to the desired material. Preparation of **7d** arises from Luche reduction of **9** to give **10** followed by Claisen rearrangement with $CH_3C(OEt)_3$ to afford **11**. Treatment affords **7d** as a mixture of keto and enol forms of the desired structure (eq 3). Finally, **7e** arises from **14** (the –OTBS analog of **9**, via LDA/TosCN treatment (eq 4).

Previous work in this laboratory has demonstrated that substitution at varied positions around the ring can greatly affect the yields of aryllead(IV) coupling reactions to cyclohexanones. As shown in Scheme 2, methyl substitution at C4 or C5 of the methyl cyclohexan-2-one carboxylate template allows arylation to proceed in 65% and 74% yield, respectively. However, movement of the methyl group to the C6 position cuts the yield dramatically to 23%. Since the synthesis of the welwistatin structure would require the installation of the quaternary C12 center adjacent to the fully substituted C11 center, we set out to explore the limitations of aryllead(IV) reagents for the production of such highly congested centers. In addition, we undertook preliminary studies on the formation of enantiomerically pure (EP) cyclohexanone derivatives as possible synthetic intermediates toward the production of welwistatin in its natural form.

We first turned our focus toward the production of a simple C12 *gem*-dimethyl substrate, and known compound 15^{24} was chosen for synthesis by a non-enzymatic route (Scheme 3). Known enantiopure compound 16 was prepared from quinic acid (17) following literature procedures. ²⁵ Conjugate addition of dimethyl cuprate, followed by trapping with TMSCl afforded the expected trimethylsilyl enol ether, which was oxidized to known enone 18 with DDQ and hexamethyldisilazane. Finally, following the literature procedure, ²⁴ a second cuprate addition in the presence of methyl cyanoformate afforded desired β -ketoester 15.

Conformational rigidity has been shown to have a marked effect on arylations of simple systems. For example, Pinhey has shown that while the mono and diarylation of 2,4-pentandione proceeds sluggishly at 19% and 2.5% yields, respectively, the same conditions employed on dimedone gave diarylated product in 75-82% yields. Encouraged by these results, we focused our attention on synthesizing two bicyclic substrates for the coupling reaction studies.

The synthesis of the simpler bicyclic substrate **19** is shown in Scheme 4. From compound **18**, addition of vinyl Grignard reagent in the presence of CuBr-Me₂S affords the C12 quaternary center in a 14:1 diastereomeric ratio. Hydroboration of **20** gives the desired alcohol with concomitant reduction of the ketone to give **21**. This diol can be selectively monofunctionalized on the primary hydroxyl with ethyl chloroformate to afford **22**, and disubstituted product **23** can be recycled to **21** in good yield. Oxidation of **22**, followed by lactone formation, ²⁷ gives bicyclic product **19**, shown to exist entirely as the enol form by ¹H and ¹³C NMR.

In addition, we synthesized **25**, a bicyclic analog of **7b** containing the exocyclic double bond as a potential synthetic handle for further transformations. Starting from (S)-carvone (**26**),

diastereoselective epoxidation gives 27, which is followed by reduction with anhydrous hydrazine to afford known compound 28 in 81% yield over the two steps (Scheme 5). 28 Pivaloyl protection to 29 is followed by allylic oxidation with chromium (VI) oxide and 3,5-dimethylpyrazole, which proceeds sluggishly to give 30 in 32% yield. The resultant enone is then subjected to vinyl cuprate addition to afford 31 in good diastereoselectivity and yield. Compound 31 is subjected to hydroboration to give 32 and bis-carbonate formation to give dicarbonate 33. Oxidation of the secondary alcohol with Dess-Martin periodinone gives compound 34, which then undergoes cyclization to 25 with concomitant elimination upon treatment with potassium hydride.

As is shown in Table 1, the boron-lead exchange/coupling sequence affords desired material in good yield using both β -ketoester and β -ketonitrile substrates. In particular, the boron-lead exchange reaction was successful in generating the *m*-nitro aryllead coupling partner, and the subsequent lead arylation could be performed in yields ranging from 52-70% (entries 1, 4, 6). Moreover, the *m*-bromo aryllead reagent could also be successfully generated, and coupled to β -ketoester **7b** in 77% yield (entry 2). Earlier work from our laboratory demonstrated that the silyl protection group at the C5 center of the 2-oxo-cyclohexanenitriles and methyl cyclohexan-2-one carboxylates is critical to the stereochemistry of the newly-formed chiral center. ²⁹

Unfortunately, standard conditions for arylation employing p-methoxyphenyllead triacetate 30 with either 15 and pyridine or the preformed sodium salt of 15 at both room temperature and conventional heating to 60 °C proved fruitless and forced us to explore a number of modified reaction conditions.

Unpublished work in our lab suggested that, although monosubstitution at C6 afforded poor yields of coupled product, use of microwave irradiation rather than conventional heating could modestly increase the formation of desired material. Inspired by the work of Moloney and coworkers, we also decided to explore the use of different bases to act as lead ligands in place of pyridine. The Oxford team demonstrated that the use of DMAP, 1,10-phenanthroline, and in the most successful case, a pre-made DABCO-lead reagent complex can dramatically increase the rate of arylation. It seems reasonable to suggest that bases such as 1,10-phenanthroline may be helpful in driving the aryllead reaction to completion by binding to the metal center in a bidentate fashion that can drive the aryl and carbon acid groups from their initial apical positions to the necessary *cis*-type apical/equatorial positions required for reductive elimination (coupling) of the organic fragments. 32

Interestingly, while no reaction conditions were able to transform **15** to the desired arylation product, a number of reaction conditions gave small amounts of diarylated compound **36**, as well as trace amounts of both diastereomers of the C3 monoarylated compound (Scheme 6). The most successful of these reactions was in the presence of DMAP ((CH₂Cl)₂ as solvent, microwave, 300W), which afforded the diarylated product in 25% yield. Small amounts of diarylated and monoarylated compounds were also seen in reactions performed at room temperature and at 65 °C, with the pre-made lead-DABCO complex and with 1,10-phenanthroline, respectively. The relatively large amount of diarylated compound compared to monoarylated compound was not surprising, as the second arylation proceeds much more rapidly due to enhanced proton acidity.

Likewise, no arylation conditions were successful on bicyclic carbon acids **19** and **25**. In addition, attempts to arylate with palladium or copper catalysis, or bismuth reagents, ³³ also proved unsuccessful. Thus, our original observation would seem to hold true - substitution at the adjacent center to that undergoing the coupling reaction severely compromises the aryllead (IV) reaction, to the point where the transformation is not synthetically useful.

In conclusion, lead-mediated arylations that were previously seen as challenging due to varied substitution on the aryl coupling partner can be achieved via an efficient boron-lead exchange protocol. In addition, our studies have shown that while lead-mediated arylation seemed a plausible strategy for the establishment of diastereoselectivity at C11 of 1, it does not prove successful in more sterically hindered systems.

Experimental Section

Ethyl 3-[5-(tert-butyldiphenylsilyloxy)-cyclohex-1-enyl]-3-methyl-butyrate (11)

A catalytic amount of propionic acid (1 drop) was added to a mixture of compound **10** (450 mg, 1.14 mmol) and triethyl orthoacetate (5 mL) and the resulting solutions was heated at 138 °C for 8 h under conditions for the distillative removal of ethanol. When the reaction was complete (GC, TLC), unreacted orthoacetate was distilled under reduced pressure. The residue was chromatographed on silica gel with hexane/ethyl acetate (100:1) which afforded the product as a colorless oil (451 mg, 85%): R_f 0.75 (EtOAc-hexane 1/8); 1 H NMR δ 7.72 (m, 4H), 7.40 (m, 6H), 5.37 (m, 1H), 4.02 (dq, J = 7.1, 1.7 Hz, 2H), 3.94 (m, 1H), 2.21 (m, 2H), 1.88 (m, 2H), 1.76 (m, 2H), 1.56 (m, 2H), 1.16 (t, J = 7.1 Hz, 3H), 1.11 (s, 9H), 1.08 (m, 6H); 13 C NMR δ 172.0, 140.6, 135.9, 134.9, 134.8, 129.6, 127.6, 118.7, 45.5, 38.0, 34.3, 31.2, 27.2, 26.9, 24.3, 19.3, 14.4; IR (neat) 3050, 2932, 1732, 1462, 1427, 1367, 1242, 1110, 822, 702 cm $^{-1}$; HRMS for $C_{29}H_{41}O_3Si$, calcd., 465.2819, found, 465.2807.

4-(tert-Butyldiphenylsilyloxy)-2-(3-hydroxy-1,1-dimethylpropyl)cyclohexanol (12)

To a stirred solution of compound **11** (330 mg, 0.71 mmol) in dry THF (5 mL) at 0 °C was added a 1 M solution of BH₃ in THF (1.42 mL, 1.42 mmol). The mixture was stirred at 0 °C for 6 h and then at RT for 12 h. A solution of NaOH (1.88 mL, 3 M) was slowly added at 0 °C followed by a solution of H₂O₂ (1.88 mL, 30%). The mixture was stirred for another 6 h then extracted with ethyl acetate (3 X 20 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure and purified by column chromatography with hexane/EtOAc (2:1) to afford as a colorless oil (197 mg, 63%): R_f 0.32 (EtOAc-hexane 1/2); ¹H NMR δ 7.69 (m, 4H), 7.40 (m, 6H) 4.06 (m, 1H), 3.79 (m, 2H), 3.53 (dt, J = 10.5, 3.7 Hz, 1H), 3.19 (Br, 2H), 2.17 (m, 2H), 1.98 (dq, J = 10.5, 3.7 Hz, 1H), 1.75 (m, 2H), 1.68 (m, 1H), 1.49 (td, J = 14.2, 5.6 Hz, 1H), 1.33 (m, 1H), 1.12 (s, 9H), 0.97 (m, 1H), 0.91 (s, 3H), 0.85 (s, 3H); ¹³C NMR δ 136.9, 134.7, 134.5, 129.7, 127.7, 73.0, 67.7, 59.5, 45.3, 43.4, 34.8, 33.4, 32.1, 28.1, 27.2, 25.0, 19.5; IR (neat) 3335, 3071, 2933, 1427, 1389, 1265, 1110, 1045, 822, 739 702 cm⁻¹; HRMS for C₂₇H₄₁O₃Si, calcd., 441.2819, found, 441.2806.

2-[3-((tert-Butyldimethylsilyloxy)-1,1-dimethylpropyl]-4-(tert-butyldiphenylsilyloxy)-cyclohexanone (13)

Triethylamine (0.07 mL, 0.54 mmol) and TBSCl (41.27 mg, 0.27 mmol) were added to the mixture of compound **12** (120 mg, 0.27 mmol) and DMAP (34 mg, 0.27 mmol) dissolved in CH_2Cl_2 (5 mL). The mixture was stirred for 2 h and was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give an oil which was passed through a short pad of silica. Dess-Martin reagent (1.6 mL, 15% weight in CH_2Cl_2) was added to a stirred solution of the above product (360 mg, 0.65 mmol) in CH_2Cl_2 (5 mL). The solution was stirred another 2 h at RT. Saturated sodium bicarbonate solution (10 mL) containing 3 g of $Na_2S_2O_3$ was poured into the reaction and stirred for 10 min. The organic layer was separated, and washed with brine, dried over Na_2SO_4 , filtered, concentrated under reduced pressure and purified by column chromatography with hexane/EtOAc (20:1) to afford the product as a colorless oil (119 mg, 80%): R_f 0.65 (EtOAc-hexane 1/8); 1 H NMR δ 7.69 (m, 4H) 7.43 (m, 6H), 4.22 (m, 1H), 3.67 (dt, J = 7.5, 1.0 Hz, 2H) 2.97 (dd, J = 13.2, 4.5 Hz, 1H), 2.89 (dt, J = 13.2, 6.0 Hz, 1H), 2.13 (ddd, J = 13.2, 4.5, 2.7 Hz, 1H), 2.03 (m, 2H), 1.90 (m, 1H), 1.72 (m, 1H), 1.49 (m, 2H), 1.13

(s, 9H), 0.97 (m, 3H), 0.93 (s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.49 (s, 3H); 13 C NMR δ 212.8, 135.9, 135.8, 134.0, 133.9, 129.9, 127.8, 67.2, 60.1, 52.0, 42.2, 39.2, 36.4, 35.6, 33.4, 27.2, 26.2, 25.7, 24.9, 19.4, -5.1; IR (neat) 3071, 2956, 1713, 1471, 1427, 1363, 1255, 1112, 1087, 997, 836, 702 cm⁻¹; HRMS for $C_{33}H_{53}O_{3}Si_{2}$, calcd., 553.3527, found, 553.3617.

Methyl 3-[3-((tert-butyldimethylsilyloxy)-1,1-dimethylpropyl]-5-(tert-butyldiphenylsilyloxy)-2-oxo-cyclohexanecarboxylate (7d)

At 0 °C, n-BuLi (2.5M, 0.18 mL, 0.45 mmol) was added slowly to diisopropylamine (0.061 mL, 0. 46 mmol) in THF (6 mL). The reaction was kept at 0 °C for 30 min and then cooled down to -78 °C under argon. A solution of compound 13 (200 mg, 0.36 mmol) in THF (2 mL) was added dropwise and the mixture was stirred for 1 h while the temperature was held at -78 °C. Methyl cyanoformate (0.45 mmol, 0.35 mL) in THF (2 mL) was added to the reaction mixture. The reaction mixture was allowed to stir for 20 min at -78 °C and then 1h at -20 °C. The reaction was quenched with ammonium chloride and extracted with ethyl acetate (3 X 10 mL). The combined organic layers were successively washed with saturated sodium bicarbonate and brine, dried over Na₂SO₄, filtered, and concentrated to give a crude product. The residue was purified by silica gel chromatography to furnish the pure product as a colorless oil (197 mg, 90%) and a mixture of diastereomers in keto and enol forms (approximately 3:2 mixture by NMR). 1 H NMR δ 7.72 (m), 7.41 (m), 4.25 (m), 4.15 (m), 3.77 (s), 3.74 (s), 3.28 (m), 3.05 (m), 3.01 (m), 2.91 (m), 2.16 (m), 1.9 (m), 1.53 (m), 1.29 (m), 1.10 (s), 1.00 (s), 0.93 (s), 0.08 (m); ¹³C NMR δ 212.7, 207.8, 207.0, 170.1, 135.9, 134.0, 133.9, 130.1, 129.9, 127.9, 127.8, 127.7, 127.6, 67.3, 66.5, 60.2, 60.0, 54.2, 52.1, 51.9, 42.3, 39.2, 38.6, 36.6, 36.4, 35.5, 33.4, 27.2, 27.1, 26.2, 25.6, 24.9, 24.8, 19.5, 18.5, 14.4, -5.1; IR (neat) 3459, 2931, 17423, 1715, 1428, 1254, 1241, 1111, 1053, 822, 702 cm⁻¹; HRMS for C₃₅H₅₄O₅Si₂Na, calcd., 633.3402, found, 633.3431.

(4S,6R)-4-pivaloxy-6-isopropenyl-3-methyl-2-cyclohexenone (30)

3,5-Dimethylpyrazole (30.5 g, 31.8 mmol) was added a slurry of CrO₃ (31.8 g, 318 mmol, dried over P_2O_5 for 24 h) in CH₂Cl₂ at -20 °C as quickly as possible. The mixture was stirred for 20 min before a solution of compound **29** (10 g, 42.4 mmol) in CH₂Cl₂ (50 mL) was added dropwise. The reaction mixture was slowly warmed from -20 to 0 °C over 15 h. Ether (1000 mL) was added and the solids filtered off. The filtrate was washed with saturated NaHCO₃, 1 *M* HCl, saturated NaHCO₃, brine, dried over Na₂SO₄, filtered, and concentrated to give a crude product. The residue was purified by silica gel chromatography with hexane/ether (100:5 to 100:20) to furnish the pure product as a colorless oil (3.39 g, 32%): [α]_D -29.2 (c 2.70, MeOH); α ₂R₂ (EtOAc-hexane 4/1); α ₃H NMR α ₄ 5.92 (m, 1H), 5.46 (m, 1H), 4.92 (m, 1H), 4.73 (m, 1H), 3.16 (dd, α ₄ = 8.5, 4.9 Hz, 1H), 2.36 (ddd, α ₅ = 13.7, 8.5, 4.2 Hz, 1H), 2.07 (ddd, α ₅ = 13.7, 6.0, 4.9 Hz, 1H), 1.90 (s, 3H), 1.74 (s, 3H), 1.20 (s, 9H); α ₅C NMR α ₅ 198.4, 177.9, 156.6, 142.0, 128.9, 114.0, 68.6, 50.6, 39.1, 32.7, 27.2, 21.1, 20.8; IR (neat) 2974, 1730, 1680, 1480, 1397, 1277, 1147, 1034, 978, 905 cm⁻¹; HRMS for C₁₅H₂₃O₃, calcd., 251.1642, found, 251.1667.

(2R,4S,5R)-4-pivaloxy-2-isopropenyl-5-methyl-5-vinylcyclohexanone (31)

A solution of compound **30** (200 mg, 0.8 mmol) in THF (10 mL) was added dropwise to a solution of vinylmagnesium bromide (2.4 mmol, 2.4 mL of 1 M in THF) and CuBr·Me₂S (18 mg, 0.083 mmol) in THF (10 mL) at -40 °C. The mixture was stirred for 30 min at -40 °C then was poured onto saturated NH₄Cl solution. The whole mixture was extracted with ether three times. The combined organic layer was washed with saturated NaHCO₃, brine, dried over Na₂SO₄, filtered, and concentrated to give a crude product. The residue was purified by silica gel chromatography with hexane/EtOAc (100:5 to 100:20) to furnish the pure product as a white solid (222 mg, 87%): R_f 0.7 (EtOAc-hexane 1/4); mp 40-42 °C; [α]_D 79.8 (c 4.00, MeOH); ¹H NMR δ 5.70 (dd, J = 17.6, 11.0 Hz, 1H), 5.12 (m, 2H), 5.01 (m, 1H), 4.93 (m,

1H), 4.72 (m, 1H), 3.12 (dd, J = 12.3, 6.1 Hz, 1H), 2.54 (dd, J = 14.5 Hz, 2H), 2.21 (ddd, J = 14.5, 12.3, 2.5 Hz, 1H), 1.99 (ddd, J = 14.5, 6.1, 4.1 Hz, 1H), 1.67 (s, 3H) 1.27 (s, 9H) 1.06 (s, 3H); 13 C NMR δ 208.5, 177.6, 142.4, 142.2, 115.7, 114.1, 73.5, 52.7, 47.1, 45.5, 39.3, 31.7, 27.4, 24.5, 20.5; IR (neat) 2973, 1729, 1717, 1480, 1281, 1149, 1033, 1000, 925, 911, 768 cm⁻¹; HRMS for $C_{17}H_{26}O_3Na$, calcd., 301.1774, found, 301.1792.

(2R,4S,5S)-4-pivaloxy-2-(2-hydroxy-1-methylethyl)-5-(2-hydroxyethyl)-5-methylycyclohexanol (32)

To a stirred solution of compound **31** (140 mg, 0.5 mmol) in dry THF (5 mL) at 0 °C was added 1 M BH₃ in THF (1.5 mL, 1.5 mmol). The mixture was stirred at 0 °C for 6 h and then RT for 12 h. A solution of NaOH (1.33 mL, 3M) was slowly added at 0 °C followed by a H₂O₂ solution (1.33 mL, 30%). The mixture was stirred for another 6 h, then extracted with ethyl acetate (3 X 20 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure and purified by column chromatography with hexane/ EtOAc (1:1) to furnish the desired product as a 2:1 mixture of alcohol isomers (75.84 mg, 48%); R_f 0.36 (EtOAc-hexane 2/1); mp 82-83 °C; 1 H NMR δ 4.68 (d, J = 14.5 Hz, 1H), 3.75 (m, J = 8.5 Hz, 2H), 3.52 (m, 1H), 3.35 (d, J = 6.5 Hz, 2H), 2.16 (ddd, J = 12.0, 4.5, 3.0 Hz, 1H), 1.97 (m, 2H), 1.53 (m, 3H), 1.38 (m, 2H), 1.19 (m, 9H), 0.91 (d, J = 7.0 Hz, 3H), 0.83 (s, 3H); 13 C NMR δ 117.8, 76.5, 76.3, 70.0, 63.6, 58.2, 40.7, 40.2, 40.0, 39.2, 38.3, 37.5, 37.2, 36.7, 35.5, 35.4, 27.4, 24.8, 21.0, 17.7, 16.2; IR (neat) 3306, 2962, 2931, 1724, 1705, 1480, 1462, 1286, 1160, 1032, 957, 737 cm⁻¹; HRMS for C₁₇H₃₂O₅Na, calcd., 339.2142, found, 339.2119.

(2R,4S,5S)-4-pivaloxy-2-(2-ethoxycarbonyloxy-1-methylethyl)-5-(2-ethoxycarbonyloxyethyl)-5-methylcyclohexanol (33)

Ethyl chloroformate (0.22 mL, 2.2 mmol) was added to a stirred solution of compound **32** (0.35 g, 1.1 mmol) and dry pyridine (5.5 mmol, 0.45 mL) in CH₂Cl₂ (10 mL) at RT under argon which was stirred overnight. The mixture was washed with saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered, and concentrated to give a crude product. The residue was purified by silica gel chromatography with hexane/EtOAc (100:20) to furnish the pure product as a colorless oil (440 mg, 87%) as a 2:1 mixture of alcohol isomers. R_f 0.7 (EtOAc-hexane 1/1); ¹H NMR δ 4.75 (m, 1H), 4.15 (m, 8H), 3.99 (dt, J = 10.8, 5.7 Hz, 1H), 2.26 (m, 1H), 1.86 (s, 2H), 1.66 (m, 5H), 1.27 (m, 6H), 1.19 (s, 9H), 1.05 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 8.0 Hz, 3H); ¹³C NMR δ 177.5, 155.5, 155.3, 75.6, 75.5, 71.4, 70.9, 67.3, 65.0, 64.0, 63.9, 39.2, 38.6, 38.5, 38.1, 36.9, 36.8, 36.7, 35.2, 33.7, 33.6, 27.3, 25.1, 24.6, 23.9, 15.6, 14.4; IR (neat) 3534, 2977, 1744, 1480, 1468, 1403, 1255, 1157, 1010, 940, 792 cm⁻¹; HRMS for C₂₃H₄₁O₉, calcd., 461.2745, found, 461.2702.

(2R,4S,5S)-4-pivaloxy-2-(2-ethoxycarbonyloxy-1-methylethyl)-5-(2-ethoxycarbonyloxyethyl)-5-methylcyclohexanone (34)

Dess-Martin reagent (2.5 mL, 15% by weight in CH₂Cl₂) was added to a stirred solution of compound **33** (460.3 mg, 1 mmol) in CH₂Cl₂ (5 mL). The solution was stirred for 3 h at RT. Saturated aqueous NaHCO₃ (10 mL containing 3 g of Na₂S₂O₃) was added and stirred for 10 min. The organic layer was separated, and washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure and purified by column chromatography with hexane/ EtOAc (2:1) to furnish the pure product as a colorless oil (366 mg, 80%): R_f0.5 (EtOAc-hexane 1/4); [α]_D 43.8 (c 2.50, MeOH); ¹H NMR δ 4.98 (m, 1H), 4.13 (m, 5H), 3.95 (m, 3H), 2.56 (m, 2H), 2.2 (m, 1H), 2.06 (m, 2H), 1.79 (m, 1H), 1.61 (m, 2H), 1.27 (m, 6H), 1.25 (s, 9H), 1.0 (s, 3H), 0.92 (d, J = 23.5, 6.9 Hz, 3H); ¹³C NMR δ 209.6, 177.1, 155.3, 154.7, 74.2, 71.5, 70.5, 64.2, 64.0, 49.4, 39.2, 35.8, 33.6, 27.3, 25.9, 24.0, 15.4, 14.4; IR (neat) 2976, 1746, 1714,

1463, 1397, 1369, 1257, 1151, 1010, 877, 792 cm⁻¹; HRMS for $C_{23}H_{39}O_9$, calcd., 459.2588, found, 459.2534.

(4S,5S)-5-pivaloxy-8-hydroxy-7-isopropylidene-4-methyl-octahydro-isochromenone (25)

A solution of compound **34** (698.3 mg, 1.52 mmol) in THF (5 mL) was slowly added to a suspension of KH (67 mg, 1.7 mol, 223.3 mg of 30% KH in mineral oil, washed three times with hexane) in THF (5 mL) and stirred at RT for 5 h. The reaction was quenched by ammonium chloride and extracted with ethyl acetate (3 X 10 mL). The combined organic layers were successively washed with saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered, and concentrated to give a crude product. The residue was purified by silica gel chromatography to furnish the desired product (320.4 mg, 46%) as a mixture of keto and enol forms (approximately 1:3 mixture by NMR). R_f 0.35 (EtOAc-hexane 1/4); ¹H NMR δ 4.71 (m), 4.42 (m), 4.17 (m), 3.88 (m), 2.84 (m), 2.34 (m), 2.23 (s), 2.04 (m), 1.85 (s), 1.70 (m), 1.38 (s), 1.26 (s), 1.23 (s), 1.2 (m), -1.71 (s); ¹³C NMR δ 177.9, 171.1, 136.7, 129.7, 128.8, 127.2, 126.3, 97.3, 75.6, 65.9, 39.2, 35.5, 33.6, 33.5, 32.0, 30.0, 29.8, 29.2, 28.8, 27.5, 27.3, 27.1, 26.2, 23.6, 23.0, 22.9, 21.0, 20.8, 20.7, 14.4, 13.7, 13.6; IR (neat) 3441, 2973, 1730, 1633, 1594, 1480, 1417, 1294, 1156, 1080, 1030, 892, 673 cm⁻¹; HRMS for C₁₈H₂₇O₅, calcd., 323.1853, found, 323.1841.

Gerneral procedure for organolead coupling reactions

To the boronic acid derivative (10 mmol) in chloroform (100 mL) was added successively lead (IV) tetraacetate (9.5 mmol) and mercury(II) trifluoroacetate (0.5 mmol) under argon. The reaction was warmed to 60 °C for 2 h then overnight at RT. The resulting mixture was warmed to 60 °C again for another 2 h. The premixed solution of β -ketoester (1.0 equiv) or β -ketonitrile (1.0 equiv) and pyridine (4 equiv) in CHCl₃ (20 mL), which had been stirred for 10 min, was added to the above mixture at 60 °C. The reaction was stirred for another 12 h, filtered through a bed of celite and 2 M H₂SO₄ was added to the filtrate. The aqueous layer was extracted with CHCl₃ (3 X 30 mL). The combined organic layers were successively washed with 2M H₂SO₄, H₂O, saturated sodium bicarbonate and brine, dried over Na₂SO₄, filtered, and concentrated to give a crude product. The residue can be purified by silica gel chromatography to furnish the pure product.

Methyl 1-[2-(2-allyloxyethyl)-phenyl]-5-(*tert*-butyldiphenylsilyloxy)-3-isopropylidene-2-oxocyclohexanecarboxylate (35e)

Following the general procedure used for organolead coupling reactions, the desired compound was isolated from the reaction of **7c** and **6d** as a white solid (67%): R_f 0.55 (EtOAc-hexane 1/2); mp 51-52 °C; 1H NMR δ 7.74 (m, 2H), 7.60 (m, 3H), 7.43 (m, 3H), 7.35 (m, 3H), 7.23 (m, 2H), 6.82 (m, 1H), 5.91 (ddd, J=16.1, 10.9, 5.7 Hz, 1H), 5.23 (ddd, J=13.8, 10.9, 1.4 Hz, 2H), 4.02 (m, 1H), 3.94 (m, 2H), 3.79 (s, 3H), 3.56 (dd, J=13.9, 8.2 Hz, 2H), 3.12 (dd, J=13.9, 8.2 Hz, 2H), 2.51 (m, 4H), 2.13 (m, 3H), 1.67 (m, 3H), 1.07 (m, 9H); $^{13}{\rm C}$ NMR δ 198.6, 172.5, 149.1, 139.0, 137.0, 135.9, 135.8, 134.9, 134.3, 133.8, 131.0, 129.8, 129.2, 128.1, 127.8, 127.4, 126.2, 117.0, 71.9, 70.5, 66.5, 65.5, 53.0, 43.0, 37.6, 33.5, 27.1, 23.8, 23.2, 19.3; IR (neat) 3070, 2932, 2858, 1735, 1683, 1428, 1265, 1231, 1104, 1057, 822, 703 cm -1; HRMS for ${\rm C}_{38}{\rm H}_{47}{\rm O}_{5}{\rm Si}$, calcd., 611.3187, found, 611.3121.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We wish to thank the NIH (CA98878) for generous support of this work. Purchase of the 600 MHz NMR used in these studies was supported by funds from the National Institutes of Health (S10RR019918) and National Science Foundation (CHE-0342912).

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B(OH)₂ OTBS OTBS

R₁
R₂ MeO₂C
$$\downarrow$$
 MeO₂C \downarrow MeCO₂C \downarrow MeO₂C \downarrow

Scheme 1. Coupling Partners

$$\begin{array}{c} C4\text{- or }C5\text{-Me} \\ \hline ArPb(OAc)_3 \\ \geq 65\% \\ \hline MeO_2C \\ \hline O \\ \hline \\ C6\text{-Me} \\ \hline ArPb(OAc)_3 \\ \hline \\ 23\% \\ \hline MeO_2C \\ \hline Ar \\ O \\ \hline \end{array}$$

Scheme 2. Effect of Substitution

OTBS
$$Me_{2}CuLi,$$

$$NCCO_{2}Me$$

$$MeO_{2}C$$

$$O$$

$$18$$

$$15$$

Scheme 3. Synthesis of EP 15

18
$$\frac{\text{H}_2\text{C=CHMgBr, Cu(I)}}{82\%}$$
 07BS $\frac{\text{BH}_3}{96\%}$ 21 OH $\frac{\text{EtOCOCI}}{75\%}$ $\frac{\text{K}_2\text{CO}_3}{\text{MeOH}}$ $\frac{\text{NaH}}{88\%}$ 0 OR $\frac{\text{NaH}}{88\%}$ 22 R = H, 66% 23 R = CO₂Et, 12%

Scheme 4. Synthesis of EP 19

$$\begin{array}{c} OR_1 \\ P_2C = CHMgBr, \\ Cu(I) \\ R_2 \\ \hline \end{array}$$

$$\begin{array}{c} OPV \\ R_2 \\ \hline \end{array}$$

$$\begin{array}{c} OPV \\ R_2 \\ \hline \end{array}$$

$$\begin{array}{c} OPV \\$$

Scheme 5. Synthesis of EP 25

Scheme 6. Arylation of 15

Table 1

Arylation with Substituted Aryllead(IV) Reagents			
OSiR ₃ EWG OSiR ₃ EWG R EWG Ar O			
7a	а-е 6а	-d	35 a-g
Entry	Substrate	Boronic Acid	Product (yield, %)
1	7a	6с	35a (70)
2	7b	6b	35b (77)
3	7c	6a	35c (72)
4	7c	6с	35d (67)
5	7c	6 d	35e (67)
6	7d	6с	35f (52)
7	7e	6d	35g (78)