

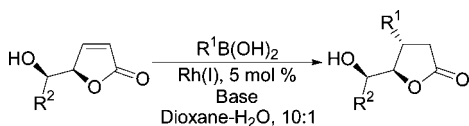
Stereoselective Rhodium-Catalyzed Conjugate Addition of Boronic Acids to Unprotected δ -Hydroxy- γ -butenolides. Synthesis of (-)-7-Oxamuricatacin and β -Substituted Derivatives

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The chiral δ -hydroxy- γ -butenolide moiety is widely found among biologically active natural products. We report herein the stereoselective synthesis of β -substituted analogues of these compounds by the Rh^I -catalyzed conjugate addition of boronic acids to chiral δ -hydroxy- γ -butenolides, easily prepared from the chiral pool. The reaction takes place with high trans diastereoselectivity without protection of the hydroxyl group. The three-step syntheses of (-)-7-oxamuricatacin ($R^1 = H$, $R^2 = CH_2-O-C_{10}H_{21}$) and of new β -substituted 7-oxamuricatacin analogues ($R^1 = \text{aryl, vinyl}$) is reported.

The chiral δ -hydroxy- γ -butenolide moiety is widely found among natural products which show diverse biological activities. For example, some of these compounds have been identified as flavor constituents in wine, sherry, and tobacco smoke;¹ 5-hydroxy- γ -decalactone (L-Factor), isolated from cultures of *Streptomyces griseus*, reveals autoregulatory properties;² and some others are cytotoxic.³ One of the latter, 5-hydroxy- γ -heptadecalactone (muricatacin), isolated from seeds of *Annona muricata*,⁴ an annonaceous acetogenin derivative, shows important cytotoxic activity on human tumor cell lines.³

Stimulated by their biological activity, various synthetic strategies have been developed for this class of compounds.⁵ In addition, many of these molecules have been used as starting materials for the synthesis of other complex biologically relevant natural products.⁶ Some unnatural analogues have been also prepared and evaluated for their antitumor activities. In particular, 7-oxamuricatacin has been reported as a more potent and selective antitumor compound than muricatacin.⁷

The search for new analogues with enhanced pharmacological properties requires the development of new synthetic methods able to increase the structural complexity in a straightforward fashion.⁸ Thus, for example, the avoidance of protection–deprotection steps in the synthetic strategy and the sequential stereoselective formation of various C–C or C–X bonds in a tandem process are welcome advantages. The conjugate addition of organometallic reagents to electron-deficient alkenes, one of the main synthetic methods for C–C bond formation, may constitute a useful procedure toward these ends.

Among the different types of conjugate additions, the reaction of aryl- and alkenylboronic acids under Rh^I catalysis, the Miyaura reaction,⁹ has become increasingly popular.¹⁰ Compared with other more traditional methods, such as organocuprate chemistry, the Rh^I -catalyzed conjugate addition of organoboronic acids enjoys more environmentally benign conditions, as the reactions can be carried out in water-containing solvents, the heavy metal is used in catalytic amounts, and the boron reagents and side products are of low toxicity, which becomes especially relevant in large-scale operations. Additionally, many aryl- and alkenylboronic acids are commercially available or can be easily prepared by a variety of methods.¹¹ Furthermore,

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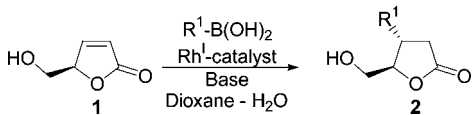
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TABLE 1. Rh^I-Catalyzed Addition of R¹B(OH)₂ to **1**. Synthesis of **2**^a



entry	R ¹	base	2 , dr ^b (yield, %) ^c
1	C ₆ H ₅	LiOH	2a , 85:15 (85)
2	C ₆ H ₅	K ₃ PO ₄	2a , 80:20 (80)
3	C ₆ H ₅	Ba(OH) ₂	2a , 95:05 ^d (90)
4	C ₆ H ₅	Et ₃ N	2a , 95:05 ^d (90)
5	C ₆ H ₅	CsF	2a , 95:05 ^d (90)
6 ^e	C ₆ H ₅	Et ₃ N	2a , 95:05 ^d (90)
7 ^f	C ₆ H ₅	Et ₃ N	2a , 70:30 (60)
8	<i>p</i> -F-C ₆ H ₄	Ba(OH) ₂	2b , 95:05 ^d (85)

^a Reactions carried out at room temperature with 0.2 mmol of **1**, 2.0 equiv of R¹B(OH)₂, and 1.0 equiv of base with 5 mol % of [(cod)RhCl]₂ with respect to **1** in 0.5 mL of dioxane–H₂O (10:1) unless otherwise stated. ^b Diastereomeric ratio determined by integration of the ¹H NMR signals of the reaction crudes. ^c Combined yield of diastereomers after column chromatography on silica gel. ^d Only one diastereomer observed by ¹H NMR (CDCl₃, 200 MHz). ^e The reaction was carried out with 5 mol % of [(cod)₂Rh]BF₄. ^f The reaction was carried out in dioxane–H₂O (8:2).

the reaction is tolerant of a wide range of functional groups, and in particular, it is possible to carry out the reactions in the presence of unprotected hydroxyl groups. This feature may also provide a means of stereocontrol for the conjugate addition step, either by chelation of the metal center (syn addition) or by steric hindrance to the approach of the nucleophile (trans addition).¹² In this regard, we have been interested in the study of the substrate-controlled stereoselectivity of this type of transformation in the presence of free OH groups either for cyclic¹³ or acyclic compounds.¹⁴

We report herein our results on the stereoselective Rh^I-catalyzed conjugate addition of aryl- and alkenylboronic acids to unprotected δ -hydroxy- γ -butenolides leading to β -substituted-7-oxamuricatacin derivatives.

At the beginning, we focused our attention in butenolide **1** (Table 1). This compound, easily derived from the chiral pool,¹⁵ has been widely used as starting material for the stereocontrolled synthesis of molecules bearing multiple stereocenters. Previously reported methods for the stereoselective functionalization of the β -carbon of compound **1** by the conjugate addition of carbon nucleophiles have required prior protection of the OH-group.¹⁶

Initial screening of reaction conditions using PhB(OH)₂ found (Table 1) that best results in yield and diastereoselectivity were

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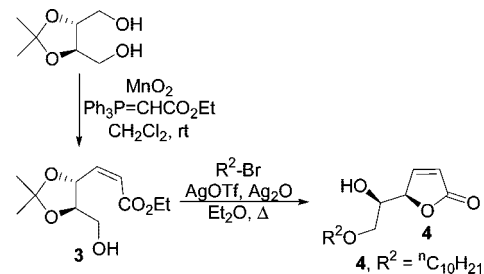
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SCHEME 1. Two-Step Synthesis of δ -Hydroxybutenolide **4**



obtained when using either Ba(OH)₂, Et₃N, or CsF as base, dioxane–H₂O (10:1) as solvent, and [(cod)RhCl]₂ as catalyst (entries 1–5). No difference was observed when the catalyst was replaced by [(cod)₂Rh]BF₄ (entry 6), and a loss of diastereoselectivity and yield was noted when the amount of water in the reaction medium was increased (entry 7). The results were extended to *p*-fluorophenylboronic acid (entry 8), as an example of electron-withdrawing substituted aryl nucleophile. In all cases, the corresponding trans isomers **2** were obtained as the major reaction products.^{17,18}

It is worth mentioning that the stereoselective synthesis of compounds **2** has also been reported by the Rh^I-catalyzed addition of boronic acids to open-chain OH-free γ,δ -oxygen-substituted α,β -enoates.¹⁴ However, the diastereoselectivity in the synthesis of compounds **2** starting from butenolide **1** reported herein (Table 1, entries 3–5) is higher than when using methyl (4*S*)-(E)-4,5-dihydroxypent-2-enoate as starting material.

Next, with the synthesis of 7-oxamuricatacin derivatives in mind, we turned our attention to butenolide **4**. It was synthesized (Scheme 1) from (–)-2,3-*O*-isopropylidene-*D*-threitol in a highly efficient two-step procedure consisting of a combined mono-oxidation and *Z*-selective Wittig reaction leading to **3**, followed by reaction of **3** with decyl bromide in the presence of AgOTf and Ag₂O. The latter transformation gave rise to **4** in a tandem etherification–acetal hydrolysis–lactonization step.¹⁹

Under the previously optimized conditions for the reaction of **1** with phenylboronic acid under Rh^I catalysis, the reactions of **4** were carried out (Table 2) with phenylboronic acid (entry 1) and arylboronic acids with para electron-accepting (entry 2), electron-donating (entries 3, 4), and ortho (entry 4) substituents, as well as vinylboronic acids (entries 5, 6), with selective generation of the 3,4-*trans* compounds **5** in all cases.

The stereochemical outcome of the reactions gathered in Tables 1 and 2 can be understood (Scheme 2) assuming that diastereoselection takes place upon complexation of the R¹-Rh^I nucleophile with the C=C bond of the substrates **1** or **4** and subsequent formation of an oxo- π -allyl-Rh^I intermediate, which may be the rate-limiting step of the catalytic cycle.¹⁰ Addition of the nucleophile from the less hindered diastereotopic face of the cycle affords the final products **2** or **5** with a *trans* relative stereochemistry between the new substituent at β -position and the original γ -hydroxylic chain.

(17) The stereochemical assignment of compound **2a** was carried out by acetylation to (AcCl, Et₃N, CH₂Cl₂) and comparison of the NMR data with those previously reported. See: Ha, H.-J.; Yoon, K.-N.; Lee, S.-Y.; Lim, M.-S.; Yim, Y.-G. *J. Org. Chem.* **1998**, *63*, 8062.

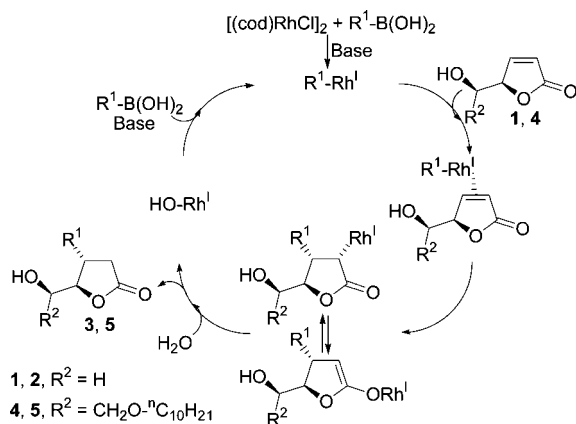
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TABLE 2. Rh^I-Catalyzed Addition of R¹B(OH)₂ to **4**. Synthesis of **5**^a

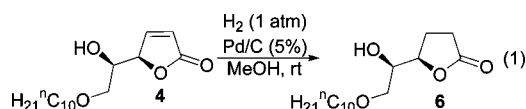
entry	R ¹	5 , dr ^b (yield, %) ^c
1	C ₆ H ₅	5a , 95:05 ^d (95)
2	<i>p</i> -CF ₃ C ₆ H ₄	5b , 95:05 ^d (80)
3	<i>p</i> -MeOC ₆ H ₄	5c , 95:05 ^d (85)
4	<i>o</i> -MeOC ₆ H ₄	5d , 95:05 ^d (75)
5	(<i>E</i>)-C ₆ H ₄ CH=CH	5e , 95:05 ^d (80)
6	(<i>E</i>)- ⁿ C ₆ H ₁₃ CH=CH	5f , 95:05 ^d (70)

^a Reactions carried out at room temperature with 0.2 mmol of **4**, 2.0 equiv of R¹B(OH)₂ and 1.0 equiv of Ba(OH)₂ with 5 mol % of [(cod)RhCl]₂ with respect to **4** in 0.5 mL of dioxane-H₂O (10:1).
^b Diastereomeric ratio determined by integration of the ¹H NMR signals of the reaction crudes. ^c Yield of the isolated product after column chromatography on silica gel. ^d Only one diastereomer observed by ¹H NMR (CDCl₃, 200 MHz).

SCHEME 2. Proposed Mechanism for the Rh^I-Catalyzed Additions of Boronic Acids to δ -Hydroxybutenolides **1** and **4**

Several previous works have reported that conjugate addition of nucleophiles to δ -hydroxy- γ -butenolides may take place with racemization at γ -position, due to the possibility of deprotonation–reprotonation of the starting materials. However, this was not the case in the Rh^I-catalyzed conjugate addition of boronic acids described herein, as evidenced in the reactions of compound **4**, which did not give rise to the formation of diastereomers.

Finally, in addition to the synthesis of the β -substituted 7-oxamuricatacin compounds **5**, reduction of the C=C bond in **4** (H₂, Pd/C, MeOH) gave rise to (–)-7-oxamuricatacin (**6**), which was prepared in three steps from 2,3-di-*O*-isopropylidene-threitol (eq 1).



In conclusion, as exemplified for (–)-7-oxamuricatacin and 7-oxamuricatacin analogues, we have developed a new entry to δ -hydroxy- γ -butenolides and a straightforward catalytic stereoselective procedure for the synthesis of δ -hydroxy- γ -butenolides substituted at the β -position by aryl and alkenyl

groups in three steps from commercial precursors, with no need of protection–deprotection steps. Variations in the R¹ and R² substituents may allow for the rapid synthesis of related compounds useful as starting materials for the synthesis of other targets.

Experimental Section

(*Z*)-(4*R*,5*R*)-3-(5-Hydroxymethyl-2,2-dimethyl[1,3]dioxolan-4-yl)acrylic Acid Methyl Ester (**3**). A mixture of (–)-2,3-*O*-isopropylidene-D-threitol (500 mg, 3.08 mmol), (methoxycarbonylmethylene)triphenylphosphorane (1.54 g, 4.62 mmol), and manganese dioxide (5.36 g, 61.66 mmol) in CH₂Cl₂ (10 mL) was stirred for 24 h at room temperature. Filtration through a Celite pad, washing with CH₂Cl₂ (10 mL), and solvent removal in vacuo gave an orange oil which was purified by column chromatography (hexane/ethyl acetate, 7:3) to afford **3** in 80% yield: ¹H NMR (CDCl₃, 200 MHz) δ 6.25 (dd, ³*J* = 11.7 Hz, ³*J* = 8.2 Hz, 1H), 5.94 (t, ³*J* = 11.7 Hz, 1H), 5.34 (t, ³*J* = 7.3 Hz, 1H), 3.94–3.55 (m, 6H), 1.44 (s, 6H); ¹³C NMR (CDCl₃, 50.5 MHz) δ 166.9, 146.9, 121.8, 109.8, 80.9, 73.8, 61.5, 51.9, 26.9, 26.9. Anal. Calcd for C₁₀H₁₆O₅: C, 55.55; H, 7.46. Found: C, 55.72; H, 7.29.

6-*O*-Decyl-2,3-dideoxy-2,3-dehydro-D-threo-hexono-1,4-lactone (**4**). To a stirred solution of **3** (946 mg, 4.38 mmol) in dry Et₂O (12 mL) were added successively Ag₂O (2.54 g, 10.95 mmol), AgOTf (281 mg, 1.09 mmol), and 1-decyl bromide (4.54 mL, 21.90 mmol). The mixture was stirred under reflux for 7 h and then filtered and evaporated. The residue was purified by column chromatography (hexane/ethyl acetate, 3:2) to give **4** in 74% yield: ¹H NMR (CDCl₃, 200 MHz) δ 7.52 (d, ³*J* = 5.7 Hz, 1H), 6.15 (dd, ³*J* = 5.7 Hz, ⁴*J* = 1.9 Hz, 1H), 5.22–5.10 (m, 1H), 4.05–3.92 (m, 1H), 3.64–3.36 (m, 4H), 1.66–1.48 (m, 2H), 1.36–1.07 (m, 14H), 0.87 (t, ³*J* = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 50.5 MHz) δ 172.8, 153.9, 122.1, 83.8, 71.8, 70.4, 70.3, 31.8, 29.4, 29.4, 29.3, 29.3, 26.1, 22.6, 14.1. Anal. Calcd for C₁₆H₂₈O₄: C, 67.57; H, 9.92. Found: C, 67.78; H, 9.75.

General Procedure for the Rh^I-Catalyzed Conjugate Addition Reactions: Synthesis of Compounds **2** and **5**. To a mixture of R¹B(OH)₂ (2.0 equiv) and [Rh(cod)Cl]₂ (0.05 equiv) under Ar was added a solution of the starting material **1** or **4** (0.11 mmol) in dioxane–H₂O (10:1, 0.5 mL) followed by the base (1.0 equiv). The mixture was stirred at 25 °C for 18 h and filtered over a Celite pad covered with MgSO₄. The Celite pad was rinsed with Et₂O. Evaporation under vacuum afforded the crude reaction products, which were purified by column chromatography (hexane/ethyl acetate, 7:3).

(4*S*,5*R*)-5-Hydroxymethyl-4-phenyldihydrofuran-2-one (**2a**): ¹H (CDCl₃, 200 MHz) δ 7.47–7.21 (m, 5H), 4.49 (dd, ³*J* = 6.9 Hz, ³*J* = 2.0 Hz, 1H), 3.94–3.76 (m, 2H), 3.61–3.28 (m, 4H), 3.08 (dd, ²*J* = 17.8 Hz, ³*J* = 9.8 Hz, 1H), 2.68 (dd, ²*J* = 17.8 Hz, ³*J* = 9.8 Hz, 1H), 1.63–1.43 (m, 2H), 1.36–1.15 (m, 14H), 0.89 (t, ³*J* = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 50.5 MHz) δ 175.9, 139.9, 129.0, 129.0, 127.5, 127.5, 127.0, 85.6, 71.5, 71.3, 69.7, 42.4, 36.9, 31.7, 29.4, 29.3, 29.3, 29.2, 25.9, 22.5, 14.0. Anal. Calcd for C₂₂H₃₄O₄: C, 72.89; H, 9.45. Found: C, 73.10; H, 9.29.

¹H NMR (CDCl₃, 200 MHz) δ 7.45–7.21 (m, 5H), 4.61–4.48 (m, 1H), 3.96 (dd, ²*J* = 12.2 Hz, ³*J* = 5.9 Hz, 1H), 3.78–3.60 (m, 2H), 3.03 (dd, ²*J* = 17.7 Hz, ³*J* = 8.83 Hz, 1H), 2.78 (dd, ²*J* = 17.7 Hz, ³*J* = 10.1 Hz, 1H); ¹³C NMR (CDCl₃, 50.5 MHz) δ 176.2, 140.9, 129.1, 129.1, 127.5, 126.9, 126.9, 82.8, 63.1, 42.1, 37.2. Anal. Calcd for C₁₁H₁₂O₃: C, 68.74; H, 6.29. Found: C, 68.96; H, 6.11.

(4*S*,5*R*,6*R*)-5-(2-Decyloxy-1-hydroxyethyl)-4-phenyldihydrofuran-2-one (**5a**): ¹H NMR (CDCl₃, 200 MHz) δ 7.47–7.21 (m, 5H), 4.49 (dd, ³*J* = 6.9 Hz, ³*J* = 2.0 Hz, 1H), 3.94–3.76 (m, 2H), 3.61–3.28 (m, 4H), 3.08 (dd, ²*J* = 17.8 Hz, ³*J* = 9.8 Hz, 1H), 2.68 (dd, ²*J* = 17.8 Hz, ³*J* = 9.8 Hz, 1H), 1.63–1.43 (m, 2H), 1.36–1.15 (m, 14H), 0.89 (t, ³*J* = 6.5 Hz, 3H). ¹³C NMR (CDCl₃,

50.5 MHz): δ 176.0, 140.1, 129.2, 129.2, 127.7, 127.7, 127.1, 85.7, 71.7, 71.4, 69.9, 42.5, 37.0, 31.8, 29.5, 29.4, 29.4, 29.3, 26.0, 22.7, 14.1. Anal. Calcd for C₂₂H₃₄O₄: C, 72.89; H, 9.45. Found: C, 73.03; H, 9.55.

Hydrogenation of 4: Synthesis of (-)-7-Oxamuricatacin (6). To a stirred solution of **4** (25 mg, 0.09 mmol) in MeOH (2.5 mL) was added Pd/C(10%) (2 mg, 0.018 mmol). The suspension was hydrogenated at 2 atm for 2 h, then filtered through a Celite pad, washed with Et₂O, and evaporated. Flash chromatography (hexane/ethyl acetate, 1:1) of the residue gave **6** in 90% yield; $[\alpha]_D^{25} -30$ (c 1.0 CH₂Cl₂); ¹H NMR (CDCl₃, 200 MHz) δ 4.56 (td, ³J = 6.9 Hz, ³J = 3.7 Hz, 1H), 3.81 (td, ³J = 6.0 Hz, ³J = 3.3 Hz, 1H), 3.53 (d, 2H, ³J = 6.0 Hz), 3.47 (t, ³J = 6.5 Hz, 2H), 2.82–2.40 (m, 2H), 2.36–2.13 (m, 2H), 1.73–1.49 (m, 2H), 1.39–1.09 (m, 14H), 0.91 (t, ³J = 6.0 Hz, 3H); ¹³C NMR (CDCl₃, 50.5 MHz) δ

177.3, 79.7, 72.1, 71.8, 71.2, 31.9, 29.5, 29.5, 29.4, 29.4, 29.3, 28.3, 26.1, 23.9, 22.6, 14.1. Anal. Calcd for C₁₆H₃₀O₄: C, 67.10; H, 10.56. Found: C, 67.29; H, 10.84.

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Supporting Information Available: Preparative methods and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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