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A short and efficient synthesis of renealtins A and B

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Abstract—The total syntheses of the first examples of diarylheptanoid natural products, renealtins A (**1**) and B (**2**), isolated from *Renealmia exaltata* are described, utilizing a δ-lactone intermediate **9**. The key reactions involved are asymmetric dihydroxylation and oxy-Michael addition.

Natural products with a tetrahydrofuran core unit[1] exhibit a diverse range of biological activities including antitumor, anthelmintic, antimalarial, antimicrobial, and antiprotozoal. Due to the importance of such molecules, considerable effort has been devoted to the development of methods for the stereoselective construction of substituted tetrahydrofurans.[2] Despite the myriad of transformations that have been employed in the construction of the tetrahydrofuran moiety,[3] many possibilities remain for the development of new or improved reactions.

Brazilian medicinal plants have proved to be a rich source of compounds that might be useful for the development of new pharmaceutical agents.[4] *Renealmia exaltata*, a Brazilian medicinal plant, is known in Brazil as 'pacova-catinga' and used as a stomachic and a vermifuge. Two new diarylheptanoids, renealtins A (**1**) and B (**2**),[5] were isolated in 2002 from the seeds of the *R. exaltata* (Zingiberaceae), and their structures were elucidated using spectroscopic data. Renealtins A (**1**) and B (**2**) are the first examples of naturally occurring diarylheptanoids containing a tetrahydrofuran ring, although some diarylheptanoids possessing a tetrahydropyran ring have been reported from *Alpinia blepharocalyx*[6] and *Zingiber officinale*.[7] A single report[8] has appeared on the synthesis of these molecules. As shown in Figure 1, renealtins (**1** and **2**) possess a five-membered cyclic ether core with two aromatic side-chains.

As a part of our research program aimed at the synthesis of biologically active natural products,[9] we decided to undertake the total syntheses of renealtin A and B. The synthesis was initiated from readily available 4-hydroxy-3-methoxycinnamaldehyde **3**. The double bond in α,β-unsaturated aldehyde **3** was selectively reduced using $NaBH_4/NiCl_2{\cdot}6H_2O$[10] in $MeOH/H_2O$ at room temperature to afford the corresponding saturated aldehyde **4** in 70% yield. Under microwave irradiation conditions,[11] the reaction of aldehyde **4** with malonic acid **5** resulted in the selective formation of the β,γ-unsaturated acid **6** in 60% yield within 6 min. Treatment of acid **6** with $BF_3{\cdot}OEt_2$ in ethanol under standard conditions resulted in ester **7** in 72% yield. The 4-hydroxy group in compound **7** was protected as a TBDMS ether **8** using TBDMSCl and imidazole in DCM in 90% yield. Asymmetric dihydroxylation of **8** using ADmix-β, with concomitant lactonization gave hydroxy lactone **9** in 80% yield (92% ee). Careful reduction of lactone **9** with DIBAL-H[12] readily allowed the formation of the lactol which, without isolation, was immediately treated with Horner's phosphonate **10**[13] under basic conditions to afford the tri-substituted furan as a 4:6 diastereomeric mixture of 2,5-cis/trans isomers, **11a/11b** in an overall yield of 60%, achieving Wittig–Horner and intramolecular oxy-Michael[14] reactions in one-pot. Diastereomers **11a** and **11b** were separated by column chromatography and their structures were confirmed by spectral data. Deprotection of compounds **11a** and **11b** using TBAF provided the target molecules renealtin A, **1** and renelaltin B, **2**. The physical data of the synthetic materials were fully consistent with those reported for the natural products.[5]

In conclusion, we have achieved the total synthesis of renealtin A and B utilizing asymmetric dihydroxylation

Keywords: Natural products; Diarylheptanoids; Tetrahydrofuran ring; Oxy-Michael; Dihydroxylation.
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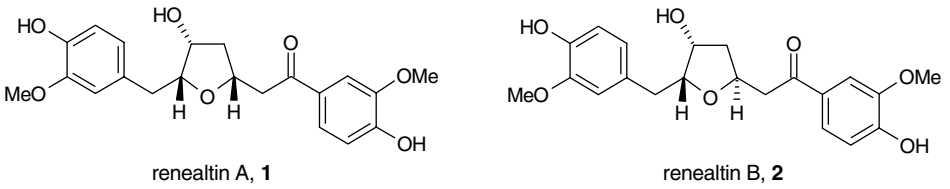
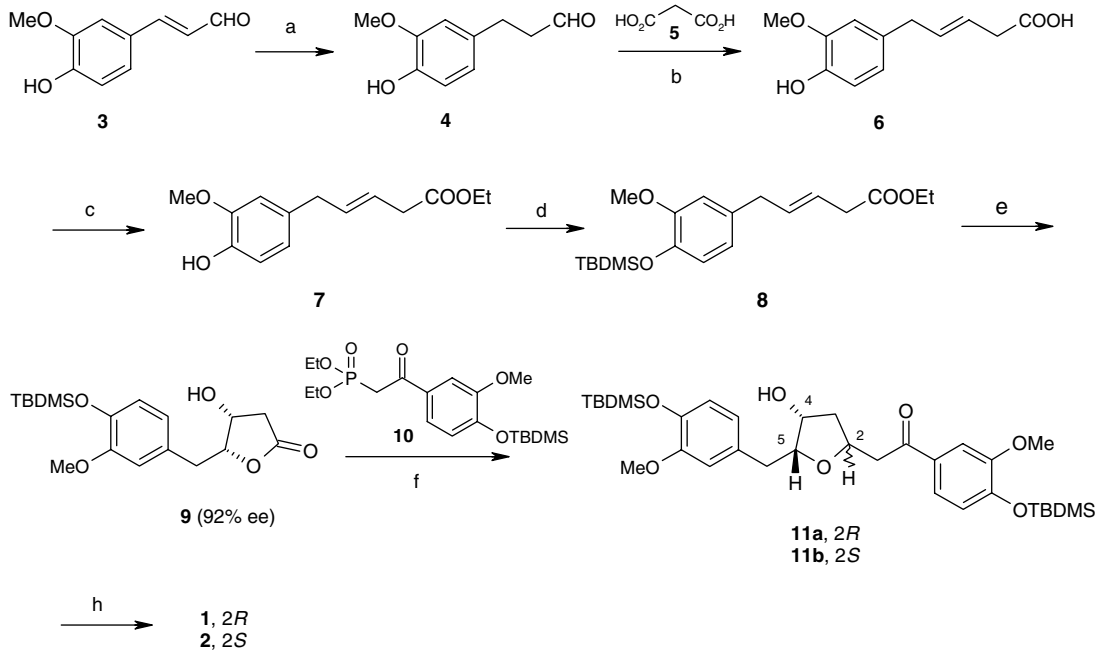


Figure 1.



Scheme 1. Reagents and conditions: (a) $NaBH_4/NiCl_2{\cdot}6H_2O/MeOH/H_2O$, rt, 50 min, 70%; (b) SiO_2, **5**, MW (600 W), 6 min, 60%; (c) EtOH, BF_3etherate, 0 °C–rt, 2 h, 72%; (d) TBDMSCl, imidazole, dry DCM, 0 °C–rt, 2 h, 90%; (e) AD-mixβ, $CH_3SO_2NH_2$, 0 °C, 14 h, 80%; (f) (i) DIBAL-H, dry DCM, −78 °C, 30 min; (ii) **10**, *n*-BuLi, dry THF, −78 °C, 12 h, overall yield 60%; (h) TBAF, dry DCM, 0 °C, 1 h, 65%.

and oxy-Michael reactions as key steps from readily available substituted cinnamaldehyde in seven steps. Further studies are underway for the synthesis of pyran derivatives and the results will be published in due course (see Scheme 1).

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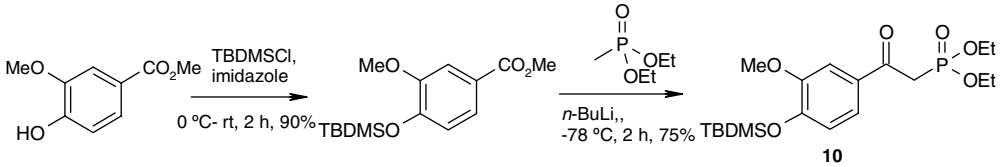

10

Diethyl [2-(4-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-3-methoxyphenyl)-2-oxoethyl]phosphonate (**10**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.53 (s, 1H), 7.50 (d, 1H, $J = 1.8$ Hz), 6.85 (d, 1H, $J = 7.9$ Hz), 4.12 (q, 4H, $J = 7.1$, 14.5 Hz), 3.88 (s, 3H), 3.55 (s, 1H), 3.48 (s, 1H), 1.3 (t, 6H, J= 7.1 Hz), 0.99 (s, 9H), 0.17 (s, 6H). ESIMS: 417 (M^++1).

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Spectroscopic data:

Ethyl (E)-5-(4-hydroxy-3-methoxyphenyl)-3-pentenoate (**7**): IR (neat): 3444, 2934, 1728, 1601, 1513, 1269, 1152, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.77 (d, 1H, $J = 9.1$ Hz), 6.63 (s, 1H), 6.61 (d, 1H, $J = 2.2$ Hz), 5.62 (m, 2H), 4.12 (q, 2H, $J = 6.7$, 14.3 Hz), 3.87 (s, 3H), 3.28 (d, 2H, $J = 6.0$ Hz), 3.02 (d, 2H, $J = 6.04$ Hz), 1.27 (t, 3H, $J = 6.8$ Hz). ESIMS: 273 (M^++Na).

(2R,3R)-2-(4-[1-(tert-Butyl)-1,1-dimethylsilyl]oxy-3-methoxybenzyl)-5-methylenetetrahydro-3-furanol (**9**): $[\alpha]_D^{25}$ +28.2 (*c* 1, MeOH). IR (neat): 3442, 2931, 2857, 1768, 1515 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.76 (d, 1H, $J = 8.3$ Hz), 6.72 (s, 1H), 6.68 (dd, 1H, $J = 1.5$, 8.3 Hz), 4.51 (m, 1H), 4.35 (m, 1H), 3.79 (s, 3H), 3.06 (m, 2H), 2.71 (dd, 1H, $J = 5.2$, 17.3 Hz), 2.48 (dd, 1H, $J = 5.2$, 17.3 Hz), 0.98 (s, 9H), 0.13 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.7, 150.9, 143.8, 129.4, 121.3, 120.9, 113.4, 85.3, 68.5, 55.5, 43.2, 39.4, 34.1, 25.6, 18.3, 14.1, −4.67. LCMS: *m*/*z*: 375.4 (M^++Na).

2-[(2R,4R,5R)-5-(4-[1-(tert-Butyl)-1,1-dimethylsilyl]oxy-3-methoxybenzyl)-4-hydroxytetrahydro-2-furanyl]-1-(4-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-3-methoxyphenyl)-1-ethanone (**11a**): $[\alpha]_D^{25}$ −6.2 (*c* 1, MeOH). IR (neat): 3442, 2929, 2856, 1671, 1590, 1512, 1465, 1286, 1160, 1036, 908, 839, 781 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.49 (d, 1H $J = 1.4$ Hz), 7.45 (d, 1H, $J = 2.2$ Hz), 6.84 (d, 1H, $J = 8$ Hz), 6.77 (br d, 1H), 6.68 (br d, 2H), 4.31 (m, 1H), 4.09, (m, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.72 (m, 1H), 3.34 (dd, 2H, $J = 2.9$, 5.8 Hz), 2.91 (m, 2H), 2.44 (m, 1H), 1.81 (dd, 1H, $J = 5.8$, 14.6 Hz), 1.01 (s, 9H), 0.98 (s, 9H), 0.17 (s, 6H), 0.12 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.2, 151.1, 150.7, 150.2, 143, 131.8, 131.2, 122.7, 121.2, 120.7, 120.2, 113.3, 111.1, 84.5, 73.7, 72.4, 55.6, 43.4,40.6, 34.6, 31.9, 29.7, 26.1, 25.7,25.6, 22.7, 18.8, −4.6, −4.5. ESIMS: 639 (M^++Na).

2-[(2S,4R,5R)-5-(4-[1-(tert-Butyl)-1,1-dimethylsilyl]oxy-3-methoxybenzyl)-4-hydroxytetrahydro-2-furanyl]-1-(4-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-3-methoxyphenyl)-1-ethanone (**11b**): $[\alpha]_D^{25}$ +9.4 (*c* 0.5, MeOH). IR (neat): 3443, 2931, 2857, 1671, 1590, 1512, 1464, 1287, 1159, 1036, 912, 839, 782 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.46 (d, 1H $J = 2.5$ Hz), 7.41 (d, 1H, $J = 6.5$ Hz), 6.8 (d, 1H, $J = 8$ Hz), 6.76 (br d, 1H), 6.67 (br d, 2H), 4.79 (m, 1H), 4.14, (m, 1H), 3.98 (m, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.36 (dd, 1H, $J = 5.8$, 16 Hz), 2.92 (m, 3H), 2.29 (dd, 1H, $J = 5.8$, 13 Hz), 1.81 (m, 1H), 0.99 (s, 9H), 0.98 (s, 9H), 0.16 (s, 6H), 0.12 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.8, 151.1, 150.7, 131.7, 131.1, 122.6, 121.2, 120.7, 120.2, 113.3, 111.1, 83.2, 73.9, 72.6, 55.4, 44.7, 41.8, 34.8, 29.6, 26.1, 25.7, 25.6, 18.4, −4.5, −4.6. ESIMS: 639 (M^++Na).

2-[(2R,4R,5R)-4-Hydroxy-5-(4-hydroxy-3-methoxybenzyl)-tetrahydro-2-furanyl]-1-(4-hydroxy-3-methoxyphenyl)-1-ethanone (*renealtin A*) (**1**): $[\alpha]_D^{25}$ +23.6 (*c* 0.5, MeOH), lit[5] $[\alpha]_D^{23}$ +22.4 (*c* 0.4, MeOH). IR (neat): 3432, 2927, 1631, 1280, 1150, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61 (dd, 1H, $J = 1.4$, 8.1 Hz), 7.50 (d, 1H, $J = 2.2$ Hz), 6.84 (d, 1H, $J = 8.1$ Hz), 6.78 (br d, 1H), 6.68 (br d, 2H), 4.31 (m, 1H), 4.09 (m, 1H), 3.91 (s, 3H), 3.76 (m, 1H), 3.74 (s, 3H), 3.54 (dd, 1H, $J = 5.8$, 13.9 Hz), 3.09 (dd, 1H, $J = 6.6$, 12.4 Hz), 2.85 (dd, 1H, $J = 7.3$, 13.2 Hz), 2.80 (dd, 1H, $J = 9.5$, 11.7 Hz), 2.54 (m, 1H), 1.77 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.2, 151.8, 147.7 147.1, 144.3, 131.8, 131.2, 123.2, 122.2, 114.4, 114.1, 113.3, 110.1, 87.5, 75.7, 73.4, 55.6, 55.5, 47.4, 41.6, 34.6. ESIMS: 411 (M^++Na).

2-[(2S,4R,5R)-4-Hydroxy-5-(4-hydroxy-3-methoxybenzyl)-tetrahydro-2-furanyl]-1-(4-hydroxy-3-methoxyphenyl)-1-ethanone (*renealtin B*) (**2**): $[\alpha]_D^{25}$ +72.7 (*c* 1, MeOH), lit[5]

$[\alpha]_D^{23}$ +73.5 (*c* 0.15, MeOH). IR (neat): 3432, 2927, 1631, 1280, 1150, 1030 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.50$ (dd, 1H, $J = 1.4$, 8.1 Hz), 7.41 (d, 1H, $J =$ 2.1 Hz), 6.83 (d, 1H, $J = 8.1$ Hz), 6.79 (d, 1H, $J = 1.4$ Hz), 6.67 (br d, 2H), 4.8 (m, 1H), 4.14 (m, 1H), 3.98 (m, 1H), 3.85 (s, 3H),3.76 (s, 3H), 3.31 (m, 1H), 3.01 (dd, 1H, $J = 7.2$, 16.1 Hz), 2.81 (dd, 1H, $J = 7.2$, 16.1 Hz), 2.77 (dd, 1H, $J = 5.8$, 13.7 Hz), 2.2 (m, 1H), 1.81 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 199.2, 154.1, 148.6, 148.2, 145.4, 132.6, 131.3, 125.1, 123.5, 116.6, 115.2, 113.2, 111.2, 84.8, 75.2, 72.6, 56.6, 46.2, 38.6, 36.5. ESIMS: 411(M^++Na).