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Efficient and Diastereoselective Synthesis of (+)-Goniobutenolide A via Palladium-Catalyzed Ene-Yne Cross Coupling–Lactonization Cascade

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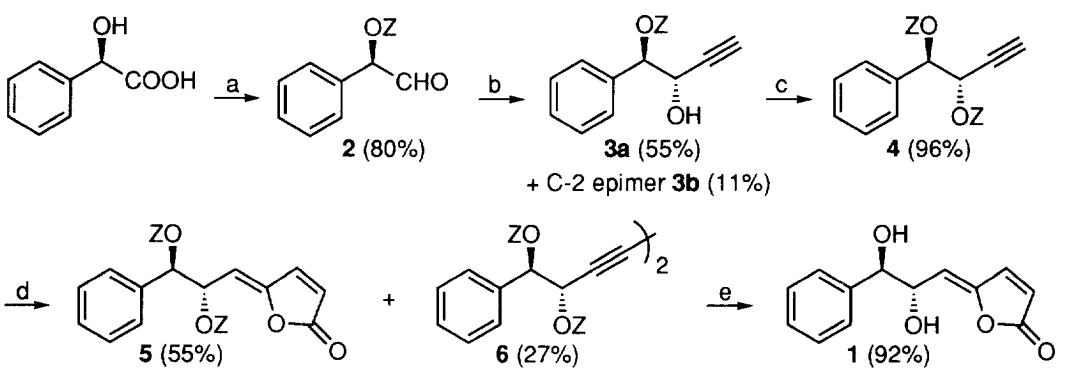
Abstract: *(+)-Goniobutenolide A was synthesized in six steps in 21.4% overall yield from (R)-mandelic acid via Pd-catalyzed ene-yne cross coupling–lactonization cascade with essentially complete control of the exocyclic alkene geometry.* Copyright © 1996 Elsevier Science Ltd

Goniobutenolide A (**1**) has been recently isolated from the ethanolic extract of the stem bark of *Goniothalamus giganteus* Hook. f. & Thomas (Annonaceae) from Thailand, and it has been shown to be marginally cytotoxic against human tumor cells.[1] Over the past few years, several syntheses of this compound have been published.[2-6] One shortcoming common to all of these syntheses is the lack of control of the exocyclic alkene geometry, the *Z*/*E* ratio ranging from 1/3 to 3/1. In view of the high efficiency and potential generality of the Pd-catalyzed ene-yne cross coupling–lactonization cascade route to (*Z*)-γ-alkylidenebutenolides with essentially complete *Z* selectivity that we have recently developed,[7,8] a synthetic route shown in Scheme 1 was envisioned. Herein we report its realization and some experimental details.

Scheme 1



Z= $SiMe_2Bu$-*t*

(a) (i) MeOH, *p*-TsOH (0.01 eq), reflux, 3h. (ii) *t*-$BuMe_2SiCl$ (1.5 eq), imidazole (2 eq), DMF, 22 °C, 12 h. (iii) *i*-Bu_2AlH (1.1 eq), Et_2O, -78 °C, 0.5 h; (b) ≡—MgCl (4 eq), THF, -78 to 22 °C, 1 h. (c) *t*-$BuMe_2SiCl$ (1.5 eq), imidazole (2 eq), DMF, 22 °C, 12h. (d) (*Z*)-3-bromopropenoic acid (2 eq), $PdCl_2(PPh_3)_2$ (0.05 eq), PPh_3 (0.2 eq), CuI (0.05 eq), Et_3N (4 eq), MeCN, 22 °C, 48 h. (e) THF-3*N* HCl, 22 °C, 6 h.

(R)-Mandelic acid was converted to aldehyde **2** via (i) esterification with MeOH and TsOH, (ii) protection with *t*-$BuMe_2SiCl$ and imidazole in DMF, and (iii) reduction with *i*-Bu_2AlH in 80% overall yield according to a literature procedure.[9] The reaction of **2** with 4 equiv of HC≡CMgCl gave a 90% combined NMR yield of a 4.3/1 mixture of the desired **3a** and its epimer **3b**, from which **3a**[10] and **3b** were isolated as pure compounds in 55 and 11% yields, respectively. The predominant formation of the desired *erythro* isomer indicates that the reaction is not of chelation control but of steric control.[11] After quantitative protection of **3a** with *t*-$BuMe_2SiCl$ and imidazole, the doubly protected diol **4** was reacted with 2 equiv of (*Z*)-3-bromopropenic acid in the presence of $Cl_2Pd(PPh_3)_2$ (5 mol%), PPh_3 (20 mol%), CuI (5 mol%), and NEt_3 (4 equiv) in MeCN at 22 °C for 48 h to produce the desired **5** in 55% yield along with diyne **6**, the amount of which corresponded to 27% of the starting alkyne **4**. Examination of the crudely isolated **5** by NMR spectroscopy indicated that it was ≥98% isomerically pure. Deprotection of the silyl group was conveniently and effectively achieved with 3*N* HCl in THF (1/1) at 22 °C for 6 h to provide a 92% yield of isomerically pure (+)-goniobutenolide A (**1**), $[\alpha]^{24}D$ +183° (*c* 1.05, $CHCl_3$), whose spectral properties shown below are indistinguishable from those reported earlier:[1,2,4-6] ^1H NMR ($CDCl_3$) δ 2.92 (bs, 2 H), 4.92 (d, *J* = 4.5 Hz, 1 H), 4.98 (dd, *J* = 8.5, 4.5 Hz, 1 H), 5.30 (d, *J* = 8.5 Hz, 1 H), 6.14 (d, *J* = 5.5 Hz, 1 H), 7.27 (d, *J* = 5.5 Hz, 1 H), 7.3 - 7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 70.61, 75.95, 112.99, 126.42 (2 C), 128.05, 128.34 (2 C), 139.02, 143.63, 150.45, 169.27; IR (Neat) 3418, 1752 cm^{-1}. The overall yield for the six-step synthesis of **1** from (R)-mandelic acid is 21.4%.

It should be emphasized here again that, in addition to proper selection of solvent,[7] *i.e.*, MeCN, the amount of PPh_3 relative to Pd is critically important for obtaining **5** from **4** in the yield indicated above. Both $Cl_2Pd(PPh_3)_2$ + 4 PPh_3 and $Pd(PPh_3)_4$ + 2 PPh_3 were satisfactory and comparable to each other, whereas the use of $Cl_2Pd(PPh_3)_2$,[8] $Pd(PPh_3)_4$,[7] or $Cl_2Pd(PPh_3)_2$ + 2 PPh_3[7] led to the formation of **5** only in 20-30% yields. On the other hand, the use of more than 6 equiv of PPh_3 relative to Pd did not further improve the yield of **5**. These results not only further support our previous conclusion[7] that the amount of PPh_3 is critically important but also indicate that optimization with respect to the PPh_3/Pd ratio may be needed for any given case. Further efforts are being made to explore the synthetic utility of the Pd-catalyzed cross coupling–lactonization cascade.

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(10) **3a**: $[\alpha]^{28}D$ -62° (*c* 11, CH_2Cl_2): ^1H NMR ($CDCl_3$) δ -0.10 (s, 3 H), 0.08 (s, 3 H), 0.91 (s, 9 H), 2.28 (d, *J* = 7.2 Hz, 1 H), 2.38 (d, *J* = 2.2 Hz, 1 H), 4.38 (ddd, *J* = 7.2, 4.8, 2.2 Hz, 1 H), 4.76 (d, *J* = 4.8 Hz, 1 H), 7.25-7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ -5.05, -4.66, 18.19, 25.74, 67.87, 74.57, 77.40, 81.81, 127.11 (2 C), 127.95 (2 C), 127.99, 139.71; IR (neat) 3450, 3310, 1106 cm^{-1}.

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