3-1-2014

Synthetic Approach to the Psoracorylifols

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Disciplines

Chemistry

Comments

This article is published as Kraus, George A., and Pengfei Dong. "Synthetic Approach to the Psoracorylifols." *Natural Product Communications* 9, no. 3 (2014): 309-310. DOI: 10.1177%2F1934578X1400900305. Posted with permission.

NPC Natural Product Communications

2014
Vol. 9
No. 3
309 - 310

Synthetic Approach to the Psoracorylifols

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Received: January 28th, 2014; Accepted: January 30th, 2014

Core analogs of the psoracorylifols were generated by a five-step route from 2,2-dimethyl-4-cyanobutanal.

Keywords: Psoracorylifols, Nitrile, Ketal.

Psoracorylifols A–C (**1**–**3** in Figure 1) were isolated from the seeds of *Psoralea corylifolia* L. (Fabaceae), a well-known traditional Chinese medicine, which has been applied to cure gynecological bleeding, vitiligo and psoriasis [1]. They were recently identified and characterized by Yue and coworkers [2]. They reported that psoracorylifols A–C showed potent inhibitory activity against two strains of *Helicobacter pylori* with MICs of 25, 12.5 and 12.4 μg per mL, respectively. Compounds **2** and **3** were especially effective against *H. pylori*-ATCC 43504, a drug resistant strain, with activities ten times stronger than metronidazole [2]. Recently, Hashimoto and coworkers reported a synthesis of the core skeleton of the psoracorylifols using a carbonyl ylide cycloaddition reaction as the key step [3]. We report herein a more direct and strategically very different synthetic route to psoracorylifol analogs that is readily extendable to single enantiomer synthesis.

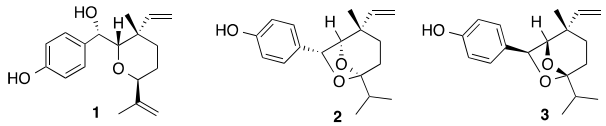
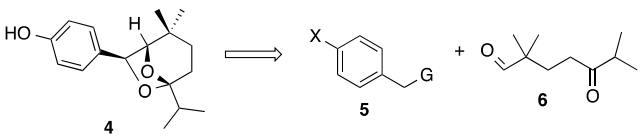


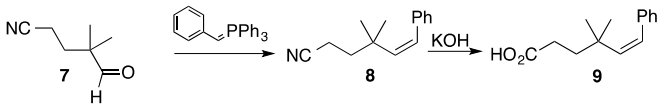
Figure 1: Structures of psoracorylifols A (**1**), B (**2**), and C (**3**).

In order to identify an efficient synthetic pathway, we initially explored the strategy shown in Scheme 1. The benzylic phosphonium salts (G = Ph_3P^+) and benzylic sulfonium salts (G = SMe_2^+) are commercially available. The keto aldehyde **6** was prepared by the Michael addition of the enol silyl ether of isobutyraldehyde with isopropyl vinyl ketone [4] in 90% yield by the method of Fleming and Newton [5]. Unfortunately, neither the phosphonium salt nor the sulfonium salt afforded the desired alkene or epoxide with **6**. Examination of the NMR spectra of the unpurified reaction suggested that intermolecular aldol-derived side reactions had intervened.



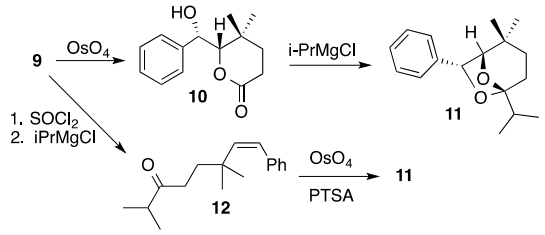
Scheme 1: Retrosynthetic analysis.

In view of the lability of **6**, we next evaluated nitrile aldehyde **7**, readily available from the base mediated reaction of isobutyraldehyde with acrylonitrile. This compound had the advantage that it could be made in 67% yield in multigram quantities according to the method of Bruson [6]. Fortunately, the reaction of benzyl(triphenyl)phosphorane with aldehyde **7** provided nitrile **8** in 65% yield after silica gel chromatography, as shown in Scheme 2. Hydrolysis of **8** with KOH in aqueous ethanol provided carboxylic acid **9** in 85% yield.



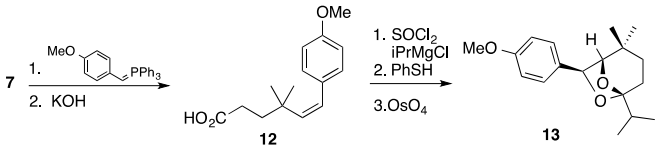
Scheme 2: Synthesis of acid **9**.

Although the resulting olefinic acid could not be epoxidized with MCPBA, it did react with osmium tetraoxide in acetone and water to afford lactone **10**, shown in Scheme 3. Lactone **10** reacted readily with isopropylmagnesium chloride to afford ketal **11** in 33% yield, after workup with ammonium chloride. After some experimentation, we found that acid **9** reacted with thionyl chloride followed by isopropylmagnesium chloride in THF to form the ketone **12** in 94% yield. Reaction of **12** with osmium tetraoxide followed by treatment with PTSA afforded **11** in 53% yield.



Scheme 3: Synthesis of **11**.

With a route to the core skeleton in hand, we targeted a closer analog by reacting **7** with 4-methoxybenzyl(triphenyl)phosphorane, followed by hydrolysis of the nitrile, as shown in Scheme 4. The resulting acid **12** was treated with thionyl chloride and the unpurified product was treated with isopropylmagnesium chloride to generate the ketone. At this point, the *cis*-styrene unit was isomerized to the *trans*-alkene using thiophenol and AIBN [7] in boiling benzene. This enone was treated with OsO_4 to furnish ketal **13** in 40% yield from **12**. Comparing the NMR spectrum of ketal **13** with that of **3**, the coupling constant for the adjacent methine protons in both compounds was less than 1 Hz. In contrast, the coupling constant for the comparable methines in compound **11** was 4 Hz.



Scheme 4: Synthesis of **13**.

Ketal **13** is available in only five steps from aldehyde **7**. This route will enable the analysis of stereoisomeric analogs of **3** in order to better understand the mechanism of action of this novel family of natural products.

Experimental

Z-4,4-Dimethyl-6-phenyl-5-hexenoic acid (9): To a solution of 4.97 g (11.46 mmol) of benzyltriphenylphophonium bromide in 60 mL of THF at 0°C, 4.6 mL (11.46 mmol) of *n*-BuLi was added dropwise. After stirring at 0°C for 1 h, 1.20 g (9.55 mmol) of nitrile aldehyde was added to the solution. The resulting solution was stirred overnight at room temperature. Sat. NH_4Cl solution was added to quench the reaction, followed by extraction with ethyl acetate. The desired nitrile product was isolated by silica gel CC, in 73% combined yield, and a *cis*:*trans* ratio of 6:1.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 – 7.21 (m, 3 H), 7.19 – 7.09 (m, 2 H), 6.58 (d, *J* = 12.7 Hz, 1 H), 5.43 (d, *J* = 12.7 Hz, 1 H), 2.31 – 2.19 (m, 2 H), 1.71 – 1.59 (m, 2 H), 0.98 (s, 6 H).

To a solution of 0.40 g (2 mmol) of nitrile in 10 mL of 4:1 ethanol and water, 0.34 g (6 mmol) of KOH was added. After the reaction mixture had been heated to reflux for 1 h, another 0.17 g (3 mmol) of KOH was added. The reaction was kept boiling for another 24 h. A 1M HCl solution was added to the cooled reaction mixture until the pH=3. Extraction with ethyl acetate gave 0.42 g (85%) of acid.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 – 7.11 (m, 5H), 6.53 (d, *J* = 12.7 Hz, 1H), 5.46 (d, *J* = 12.7 Hz, 1H), 2.40 – 2.27 (m, 2H), 1.70 – 1.57 (m, 2H), 0.94 (s, 6H).

5-Isopropyl-2,2-dimethyl-7-phenyl-6,8-dioxabicyclooctane (11): To 20 mL of a 2:1 acetone/H_2O solution with 0.22 g (1 mmol) acid and 0.45 g (4 mmol) of trimethylamine *N*-oxide (TMAO), 0.63 mL of OsO_4 in t-BuOH solution (2.5% wt. %) was added dropwise. The reaction was monitored by TLC until the starting material was gone. Saturated sodium sulfite solution was added, and the mixture was stirred for 30 min followed by extraction with dichloromethane. The resulting product was dissolved in dichloromethane, followed by 1 equiv of DCC and 10 mol % of DMAP. The reaction mixture was stirred overnight, then washed with saturated NH_4Cl solution, and brine. Silica gel CC gave the desired lactone product in 52% yield.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 – 7.24 (m, 5H), 4.81 (t, *J* = 5.3 Hz, 1H), 4.30 (d, *J* = 5.7 Hz, 1H), 2.67 (d, *J* = 5.0 Hz, 1H), 2.44 (ddd, *J* = 11.8, 8.1, 6.4 Hz, 2H), 1.65 (dt, *J* = 13.2, 8.1 Hz, 1H), 1.57 – 1.43 (m, 1H), 1.12 (s, 3H), 0.92 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): *δ* 171.4, 141.1, 128.8, 128.6 127.7, 89.4, 74.6, 35.6, 32.4, 27.6, 27.5, 20.9.

To a solution of 62 mg (0.26 mmol) of lactone in THF solution at -78°C, 0.33 mL (0.66 mmol) of isopropyl magnesium chloride solution (2 M in THF) was added dropwise. The reaction was stirred at -78°C for 5 h. Then saturated NH_4Cl solution was added to quench the reaction, followed by extraction with ethyl acetate. Prep-TLC gave 23 mg (33%) of product.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, *J* = 7.6 Hz, 2H), 7.38 – 7.18 (m, 3H), 5.25 (d, *J* = 4.6 Hz, 1H), 4.03 (dd, *J* = 4.6, 1.9 Hz, 1H), 2.11 – 1.66 (m, 4H), 1.21 – 1.13 (m, 1H), 1.11 – 1.00 (m, 9H), 0.17 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): *δ* 137.8, 128.3, 127.2, 126.5, 111.3, 86.0, 81.5, 35.4, 34.6, 30.8, 28.5, 28.0, 26.1, 17.1, 17.1.

5-Isopropyl-7-(4-methoxyphenyl)-2,2-dimethyl-6,8-dioxabicyclooctane (13)
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 – 7.16 (m, 2H), 6.82 – 6.75 (m, 2H), 4.98 (br s, 1H), 3.72 (br s, 4H), 2.00 (p, *J* = 7.0 Hz, 1H), 1.68 (dd, *J* = 8.7, 2.0 Hz, 2H), 1.58 – 1.50 (m, 1H), 1.35 – 1.28 (m, 1H), 1.05 – 0.94 (m, 9H), 0.91 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 135.5, 127.8, 113.9, 112.2, 90.1, 78.0, 55.5, 35.7, 32.8, 30.3, 26.4, 26.2, 24.6, 18.4, 17.8.

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