

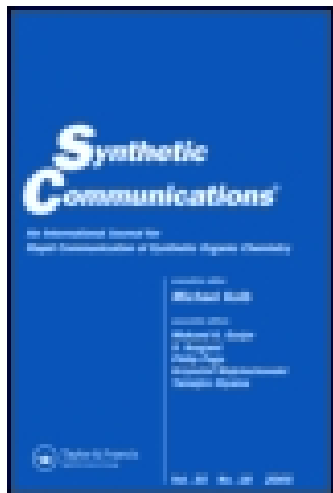
This article was downloaded by: [McMaster University]

On: 21 January 2015, At: 07:03

Publisher: Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954

Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



## Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/lcyc20>

### A Racemic Synthesis of the Novel Antibacterial Agent Juglomycin A

George A. Kraus<sup>a</sup> & Peng Liu<sup>a</sup>

<sup>a</sup> Department of Chemistry, Iowa State University, Ames, IA, 50011

Published online: 23 Aug 2006.

To cite this article: George A. Kraus & Peng Liu (1996) A Racemic Synthesis of the Novel Antibacterial Agent Juglomycin A, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:23, 4501-4506, DOI: [10.1080/00397919608003852](https://doi.org/10.1080/00397919608003852)

To link to this article: <http://dx.doi.org/10.1080/00397919608003852>

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages,

and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at <http://www.tandfonline.com/page/terms-and-conditions>

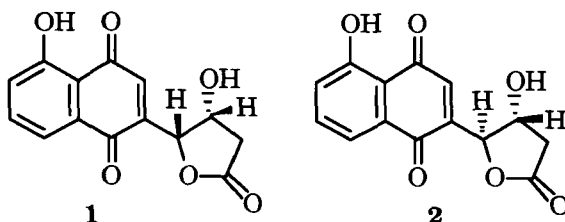
## A RACEMIC SYNTHESIS OF THE NOVEL ANTIBACTERIAL AGENT JUGLOMYCIN A

George A. Kraus\* and Peng Liu

Department of Chemistry, Iowa State University, Ames, IA 50011

**Abstract:** Juglomycin A has been synthesized in six steps from juglone.

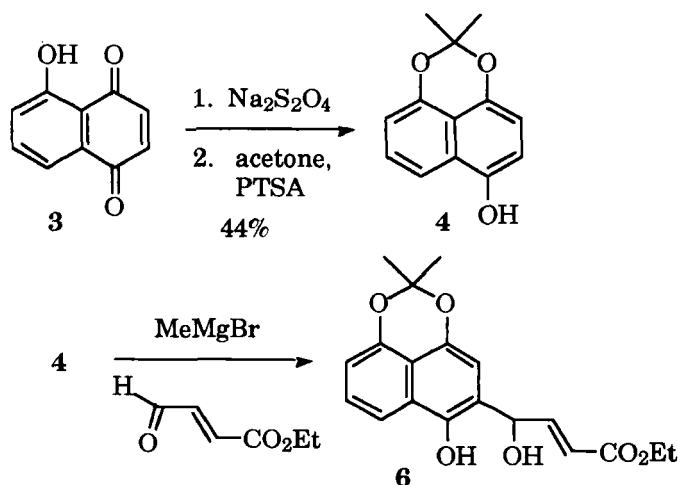
Juglomycin A (**1**) and juglomycin B (**2**) were isolated from *Streptomyces* sp. 190-2 by Ono and coworkers.<sup>1</sup> Their structures were initially determined by proton NMR studies<sup>2</sup> and later revised after an X-ray structure determination.<sup>3</sup> Syntheses of racemic **1** and **2** were reported by Giles and coworkers.<sup>4</sup> Recently, Brimble and Ireland have reported a formal synthesis.<sup>5</sup> Both **1** and **2** exhibit antibacterial activity against both Gram-negative and Gram-positive



\* To whom correspondence should be addressed.

bacteria.<sup>6</sup> In the course of developing a general synthetic route to pyranoquinone antibiotics, we identified **1** as a key intermediate. We report herein a direct synthesis of racemic juglomycin A.<sup>7</sup>

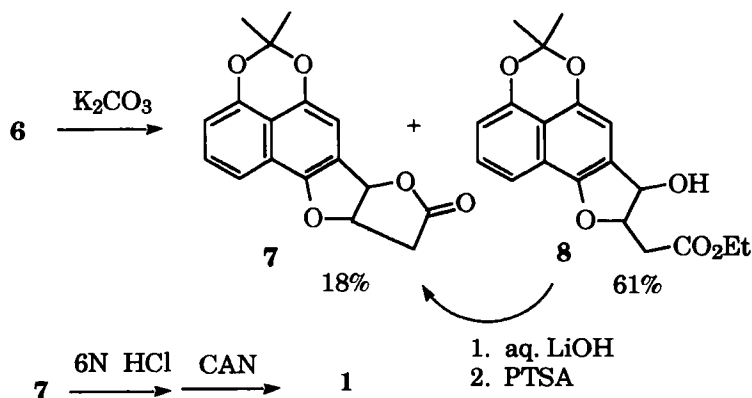
Our synthesis of **1** began with juglone (**3**) which was converted into naphthol **4**<sup>8</sup> by reduction and acetonide formation. Compound **4** was treated with methyl magnesium bromide to afford the



magnesium alkoxide which reacted with the ethyl ester of 3-formyl acrylic acid (**5**)<sup>9</sup> using the method of Casiraghi<sup>10</sup> to form ester **6** in 70% yield.

Michael addition of the phenol was effected using potassium carbonate in methanol. This produced the desired lactone **7** in 18% yield and the hydroxy ester **8** in 61% yield. We subsequently found that **8** could be transformed into **7** by hydrolysis with aqueous lithium hydroxide followed by lactonization with PTSA. The acetonide protecting group was removed using 6N HCl. Oxidation with ceric ammonium

nitrate in aqueous acetonitrile afforded juglomycin A in 56% yield from lactone **7**.



Juglomycin A can be synthesized from juglone in six steps. Each step is operationally convenient and reproducible. Since studies using juglomycin A have been impeded by its low natural occurrence, our synthetic route will allow more extensive biological evaluation of this interesting antibacterial agent.

## Experimental

### Ethyl 2',6-dihydroxynaphtho[1,8-de]-1,3-dioxin butenoic acid (**6**)

To a solution of methylmagnesium bromide (3.71 mmole) in anhydrous diethyl ether (10 mL), a solution of naphthol **4** (0.8022 g, 3.71 mmole) in diethyl ether (10 mL) was added under stirring at rt. After stirring for 20 min, the ether was removed completely under vacuum and anhydrous dichloromethane (15 mL) was added, cooled to  $-78\text{ }^{\circ}\text{C}$ , a solution of **5** (3.71

mmole) in dichloromethane was added. After stirring for 3 h the reaction mixture was warmed to rt, quenched with saturated ammonium chloride solution, extracted with dichloromethane (3 x 30 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo. The residue was chromatographed on silica gel with hexane/ethyl acetate (4:1) to give 0.907 g (71% yield) of **6** as a yellow oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.27 (t,  $J = 6.9$  Hz, 3H), 1.63 (s, 6H), 3.11-3.12 (br, 1H, exchange w/ $\text{D}_2\text{O}$ ), 4.19 (q,  $J = 6.9$  Hz, 2H), 5.59 (dd,  $J = 1.5$ ,  $J = 5.4$  Hz, 1H), 6.10 (dd,  $J = 1.5$ ,  $J = 17.1$  Hz, 1H), 6.47 (s, 1H), 7.10 (dd,  $J = 5.4$ ,  $J = 15.6$  Hz, 1H), 7.40 (t,  $J = 8.1$ , 1H), 7.73 (d,  $J = 8.1$  Hz, 1H). IR ( $\text{CHCl}_3$ ): 3640, 2941, 1733, 1616. Ms ( $m/z$ ): 343 ( $m-1$ ), 342 ( $m-2$ ) 269, 242, 214, 199, 173, 146, 118, 100, 73. CMR: 14.13, 25.07, 25.16; 60.44; 87.09, 101.56, 105.26, 109.58, 113.47, 114.90, 118.83, 120.22, 126.72; 140.62, 145.59, 146.79, 147.74, 166.34, 170.56.

**Preparation of Lactone 7** Compound **6** (0.1047 g, 0.304 mmol) was added to a rapidly stirred solution of potassium carbonate (0.5 g) in methanol (10 mL) at rt. After stirring for 36 h, the reaction mixture was acidified with 2N HCl at 0 °C and extracted with dichloromethane (3 x 20 mL). The solvent was removed in vacuo and the residue was purified by chromatography on silica gel with hexane/ethyl acetate (2:1) to give compound **8** (61%) and compound **7** (18 mg, 18%). Compound **8** was treated with LiOH in ethanol: $\text{H}_2\text{O}$  (2:1) for 24 h, acidified with 2N HCl at 0 °C, extracted with ether (3 x 15 mL), dried and concentrated in vacuo. The residue was treated with PTSA in dichloromethane for 24 h. The reaction mixture was diluted with 5 mL of  $\text{H}_2\text{O}$ , extracted with dichloromethane (3 x 15 mL), dried and concentrated in vacuo. The residue was purified by chromatography to give compound **7**.

**Compound 7:**  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.65 (s, 6H), 2.86 (dd,  $J = 7.8$ , 17 Hz, 1H), 3.16 (dd,  $J = 3.6$ , 17 Hz, 1H), 4.15-4.22 (m, 1H), 5.07-5.10 (m, 1H), 6.92 (s, 1H), 7.13 (d,  $J = 7.5$ , 1H), 7.55 (t,  $J = 8.1$ , 1H), 7.80 (d,  $J = 8.1$  Hz, 1H). IR ( $\text{CHCl}_3$ ): 2964, 1781  $\text{cm}^{-1}$ . MS ( $m/z$ ): 298, 255, 231, 70, 43.

**Compound 8:**  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.23 (t,  $J = 6.9$  Hz, 3H), 1.65 (s, 3H), 2.85 (q,  $J = 7.8$  Hz, 1H), 3.15 (dd,  $J = 3.6$  Hz), 4.15-4.22 (m, 3H), 5.08 (dd,  $J = 3.6$  Hz, 1H), 6.92 (s, 1H), 7.13 (d,  $J = 7.5$ , 1H), 7.55 (t,  $J = 8.1$  Hz, 1H), 7.81 (d,  $J = 8.4$  Hz, 1H). IR ( $\text{CHCl}_3$ ): 3397, 2997, 1616  $\text{cm}^{-1}$ . MS ( $m/z$ ): 343 (m-1), 326, 297, 269, 253, 199, 173, 145, 127, 100, 74, 55.

**Preparation of Juglomycin A** To a solution of compound **7** (61 mg) in  $\text{CH}_3\text{CN}$  (5 mL) was added 0.5 mL of 6N HCl. The reaction was heated to reflux for 6 h, cooled and concentrated in vacuo. The residue was treated with ceric ammonium nitrate for 2 h. Water (5 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 15 mL), dried and concentrated in vacuo. The residue was purified by flash chromatography with hexanes/ethyl acetate (1:1) to give 45 mg (81% yield) of **1**.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  2.70 (d,  $J = 18$  Hz, 1H), 2.90 (dd,  $J = 5.4$ , 18 Hz, 1H), 4.80 (m, 1H), 5.70 (d,  $J = 3.6$  Hz, 1H), 6.81 (s, 1H), 7.25 (d,  $J = 7.6$  Hz, 1H), 7.57-7.03 (m, 2H). IR ( $\text{CHCl}_3$ ): 3155, 2969, 1784, 1630  $\text{cm}^{-1}$ . Anal. Calcd. for  $\text{C}_{14}\text{H}_{10}\text{O}_6$ : C 61.32, H 3.68. Found: C 60.96, H 3.78.

### Acknowledgment

We thank Hoffmann-LaRoche for financial support of this research.

### References

1. Ushiyama, K.; Tanaka, N.; Ono, H.; Ogata, H. *Jpn. J. Antibiot.* **1971**, *24*, 197.

2. Tanaka, N.; Ogata, H.; Ushiyama, K.; Ono, H. *Jpn. J. Antibiot.* **1971**, *24*, 222.
3. Krupa, J.; Lackner, H.; Jones, P. G.; Schmidt-Base, K.; Sheldrick, G. M. *Z. Naturforsch. B* **1989**, *44b*, 345.
4. Giles, R. G. F.; Mitchel, P. R. K., Roos, G. H. P., Strümpfer, J. M. *M. J. Chem. Soc., Perkin Trans. 1* **1981**, 2091.
5. Brimble, M. A.; Ireland, E. *J. Chem. Soc., Perkin Trans. 1* **1994**, *21*, 3109.
6. Ushiyama, K.; Tanaka, N.; Ono, H.; Ogata, H. *Jpn. J. Antibiot.* **1971**, *24*, 197. The activity reported is modest in comparison with commercially-useful antibiotics.
7. Kraus, G. A.; Maeda, H. *J. Org. Chem.*, **1996**, *61*, 2986.
8. Dallacker, F.; Jacobs, J.; Coerver, W. *Z. Naturforsch. B*: **1983**, *38B*, 1000.
9. Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synth. Commun.* **1980**, 807.
10. Bigi, F.; Casnati, G.; Sartori, G.; Soncini, P. *J. Org. Chem.* **1988**, *53*, 1779.

(Received in the USA 20 June 1996)