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A New Approach to the Furan Degradation Problem Involving Ozonolysis of the *trans*-Enedione and Its Use in a Cost-Effective Synthesis of Eplerenone

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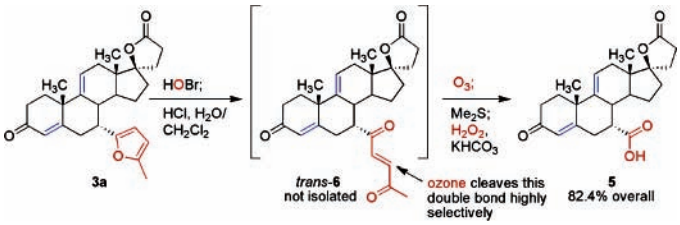
ABSTRACT



Whereas ozonization of furan 3a affords little or no carboxylic acid 5, ozonization of the corresponding *trans*-enedione 6 afforded carboxylic acid 5 in 82.4% yield (cryst., overall from furan, 100 g scale; after workup with dimethyl sulfide, followed by mildly basic hydrogen peroxide). This new approach to furan degradation is showcased in a cost-effective synthesis of eplerenone, an important new medicine for cardiovascular indications.

Since the discovery over 50 years ago that hypertension and congestive heart failure are caused by excessive levels of circulating aldosterone,[1,2] pharmaceutical research organizations have sought to discover selective aldosterone blockers.[3] In 1985, the search culminated with the discovery of eplerenone (**1**) by scientists at CIBA-Geigy.[4] However, because the dosage is relatively high, it was necessary to develop a particularly efficient manufacturing process to make this medicine accessible to the worldwide patient population at an acceptable cost. Herein is reported a cost-effective synthesis of eplerenone, the active pharmaceutical ingredient of INSPRA, a new medicine for the treatment of hypertension and congestive heart failure.[5]

In designing a synthesis of eplerenone, the principal challenge is the introduction of the carbomethoxy substituent. In the first published synthesis,[4] this was accomplished by Nagata hydrocyanation of $\Delta^{9(11)}$-canrenone (**2a**), but the stereoselectivity was at best ~4:1 7α/β, necessitating chromatography.[6] In the other published synthesis,[7] the car-

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(1) (a) Luetscher, J. A., Jr.; Deming, Q. B. *J. Clin. Invest.* **1950**, *29*, 1576. (b) Luetscher, J. A., Jr.; Neher, R.; Wettstein, A. *Experientia* **1954**, *10*, 456. (c) Reviews: Gaunt, R.; Renzi, A. A.; Chart, J. J. *J. Clin. Endocrinol. Metab.* **1955**, *15*, 621. Cross, R. J. *Am. J. Med.* **1956**, *21*, 423.

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(3) Historical review of the discovery of eplerenone: Garthwaite, S. M.; McMahon, E. G. *Mol. Cell. Endocrinol.* **2004**, *217*, 27.

(4) (a) Grob, J.; Boillaz, M.; Schmidlin, J.; Wehrli, H.; Wieland, P.; Fuhrer, H.; Rihs, G.; Joss, U.; de Gasparo, M.; Haenni, H.; Ramjoue, H. P.; Whitebread, S. E.; Kalvoda, J. *Helv. Chim. Acta* **1997**, *80*, 566. (b) Grob, J.; Kalvoda, J. U.S. Patent 4,559,332, December 17, 1985.

(5) Patent application covering this research: Pearlman, B. A.; Padilla, A. G.; Havens, J. L.; Mackey, S. S.; Wu, H. US 2003/0232981 A1, December 18, 2003.

(6) Reference 4a reports that $\Delta^{9(11)}$-canrenone undergoes hydrocyanation with Et_2AlCN stereoselectively from the α face. We have made numerous attempts to reproduce this claim and consistently observed 7α/β ratios of no more than ~4/1. See Supporting Information.

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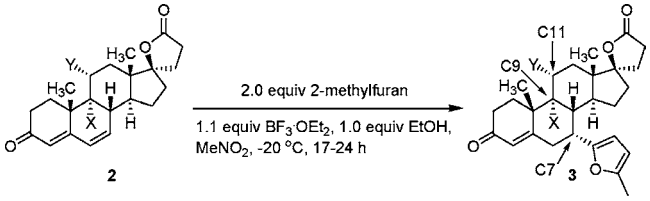
bomethoxy group was introduced stereoselectively via 4,6-bishydrocyanation of 11α-hydroxycanrenone (**2c**), but regioselective dehydration of the 11α hydroxyl was problematic. Thus, a need existed for a new method for the introduction of a carbon substituent at C-7 of the steroid nucleus.

Furylation was investigated as an alternative to hydrocyanation because the furan ring has frequently been employed as a surrogate for carboxylic acid in natural product total synthesis.[8] To effect conjugate furylation in high yield, it was necessary to employ the protic Lewis acid conditions of Poirier and Dujardin,[9] as no reaction occurred under aprotic Lewis acid conditions (e.g., $TiCl_4$, CH_2Cl_2, −30 °C). Four dienone substrates were studied (**2a**−**d**; Table 1). The

Table 1. Furylation of Steroidal Dienones



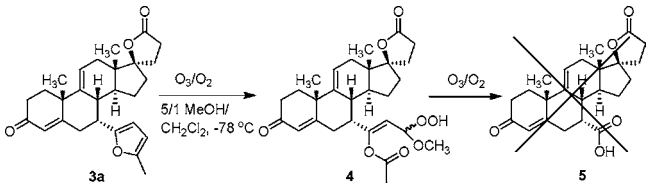
dienone		X	Y	7α/β[a]	yield[b] (%)
Δ9(11)-canrenone	**2a**	π bond		91/9	72.9
Δ9(11)-canrenone	**2a**	π bond		92/8	77.7[c]
canrenone	**2b**	H	H	78/22	69.5[d]
11α-hydroxycanrenone	**2c**	H	OH	99/1	86.2[e]
9(11)α-epoxycanrenone	**2d**	−O−		89/11	75.5

[a] Determined by LC analysis of the crude product mixture at the reaction endpoint. [b] Yield of α isomer after isolation/purification. [c] Solvent was acetonitrile. [d] Reaction time was 88 h, with double the amount of reagents. [e] Average of two runs.

most cost-effective results were obtained with $\Delta^{9(11)}$-canrenone **2a** because it is readily synthesized from crude soy sterols by a short sequence of microbiological[10] and chemical[11] steps and, although furylation was not completely stereoselective (α/β = 91/9), the β adduct is efficiently removed because it is an oil. A single crystallization of the crude product afforded crystals of **3a** that contained no more than 0.1% of the β isomer or any other impurity, with the loss of only 4.1% yield of the α isomer to the filtrate. Although 11α-hydroxycanrenone **2c** undergoes furylation more stereoselectively (α/β = 99/1),[12] the adduct **3c** is difficult to dehydrate to **3a** regioselectively.

Although furan is a popular surrogate for carboxylic acid in synthesis, no general method exists for unmasking. Two methods are most frequently used: (1) periodate/catalytic RuO_2;[13] and (2) ozonization. However, the former method requires a large molar excess of periodate, which is prohibitively expensive for commercial applications, and the latter gives highly variable yields (11−89% depending on the other functionality in the substrate).[14] Attempts to degrade furan adduct **3a** by ozonization (5/1 MeOH/CH_2Cl_2, −78 °C) resulted in rapid and selective cleavage of the distal double bond to give enol acetate **4** (as a 1:1 mixture of epimers) cleanly, followed by slower and apparently nonselective cleavage of the three remaining double bonds to give a complex mixture of polar products containing little or none of the desired carboxylic acid **5** (Scheme 1). Thus, a more

Scheme 1. Standard Ozonization Approach to Furan Degradation



effective method for the degradation of furans to carboxylic acids was needed.

Because furan **3a** can be opened to the enedione *cis*-**6**, which can be isomerized to *trans*-**6** in high yield (see Scheme 2 for conditions), degradation of both *cis*-**6** and *trans*-**6** was studied. It was found that ozone cleaves the enedione double bond of *trans*-**6** cleanly to give (after reduction of the hydroperoxide)[15] the α-ketoaldehyde methanol adduct **7** in essentially pure form. Baeyer−Villiger oxidation with basic hydrogen peroxide[16] gave the carboxylic acid **5** in 82.4% yield (crystallized, overall from **3a**, without isolation of any

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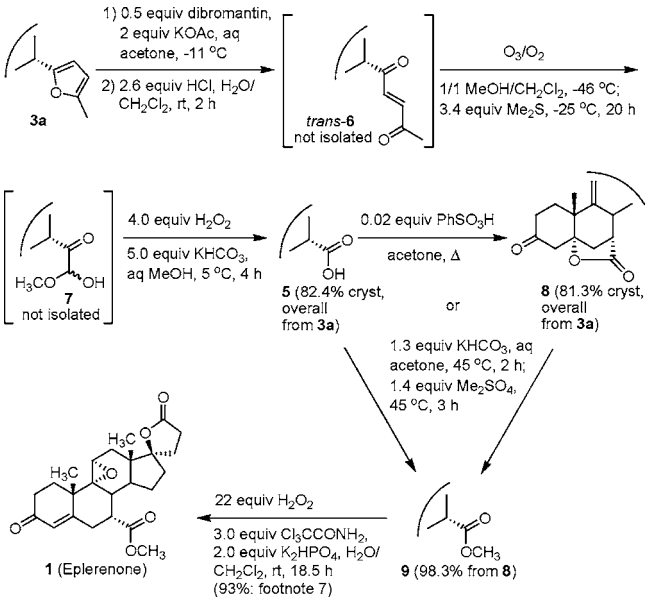
(15) The ratio of hydroxyhydroperoxide **11** to alcohol **7** in the crude ozonolysate was 31.9/68.1.

(16) (a) Nukaya, H.; Inaoka, Y.; Ishida, H.; Tsuji, K.; Suwa, Y.; Wakabayashi, K.; Kosuge, T. *Chem. Pharm. Bull.* **1993**, *41*, 649. (b) Hollingsworth, R. I. *J. Org. Chem.* **1999**, *64*, 7633.

Scheme 2. Stepwise Approach to Furan Degradation

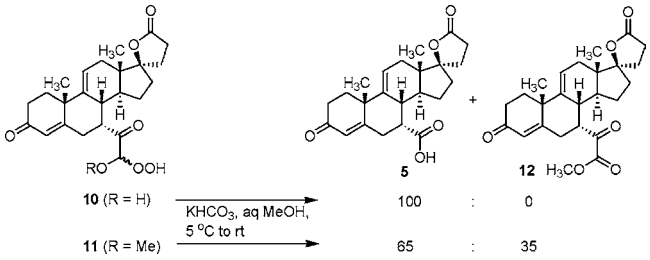


intermediates, without chromatography, 100 g scale). Careful pH control was necessary in the crystallization of the carboxylic acid to avoid isomerization to the bridged lactone **8**, as lactonization is catalyzed by both strong acid (e.g., 0.05 equiv $PhSO_3H$, CH_2Cl_2, Δ) and buffers (e.g., 0.1 equiv pyridine, CH_2Cl_2, Δ). However, bridged lactone **8** opens back to carboxylic acid **5** under the conditions of the next step (esterification). Thus, rather than isolate carboxylic acid **5**, it is preferable to allow it to convert to the bridged lactone **8** in the crystallization by intentionally adding a catalytic amount of benzenesulfonic acid. A run carried out in this manner afforded pure **8** in 81.3% yield (crystallized, overall from **3a**, without isolation of any intermediates, without chromatography, 100 g scale).[17] To complete the synthesis, either carboxylic acid **5** or bridged lactone **8** is treated with aq bicarbonate to give the carboxylic acid potassium salt, which is treated with dimethyl sulfate to give the methyl ester **9**, which is epoxidized[7] to give eplerenone **1**.

Compound *cis*-**6** underwent degradation to **5** in significantly lower yield than *trans*-**6** (86.1% vs 97.4%). This is attributed to competitive ozonolysis of the two nuclear double bonds on the basis of a set of competition experiments, which established that *cis*-**6** undergoes ozonolysis ~8 times more slowly than *trans*-**6** (−59 °C, 1:1 MeOH/CH_2Cl_2).

The unusual reductive/oxidative workup of the ozonolysate requires explanation. Workup with mildly basic H_2O_2 gave mixtures of **5** and α-ketoester **12**, formed by the dehydration of **11** (Scheme 3).[18] However, treatment of **7** with mildly

Scheme 3. Reactivity of Methoxy- vs Hydroxy-Hydroperoxide



basic H_2O_2 gave **5** cleanly, presumably via **10**. Thus, the key to clean Baeyer−Villiger cleavage is to treat the crude ozonolysate with Me_2S to reduce **11** to **7** prior to treatment with mildly basic H_2O_2.[19]

Because *trans*-enediones are highly electrophilic and ozone is also electrophilic,[20] the preference of ozone for attacking the *trans*-enedione over the more electron-rich nuclear double bonds is noteworthy. Presumably the pendant enedione is attacked selectively because it is less sterically shielded than the other double bonds. Steric effects on olefin ozonization rates have been documented.[20b,e]

In summary, an efficient process for the synthesis of eplerenone, a new medicine for the treatment of hypertension and congestive heart failure, is described. The process features a novel approach to furan degradation involving opening/isomerization to the *trans*-enedione, ozonization/reduction to the α-ketoaldehyde, and Baeyer−Villiger oxidation to the carboxylic acid. The success of this approach to furan degradation should encourage the broader use of furan as a synthon for carboxylic acid in organic synthesis.

Acknowledgment. We are grateful to our Pfizer colleagues Dr. Stephen H. Grode for spectroscopic support, Dr. John G. Hoogerheide for analytical support, and Dr. Thomas A. Runge for project direction.

Supporting Information Available: Experimental procedures; compound characterization data; ^{13}C and ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Alternatively, methoxyhydroperoxide **4** can be degraded to lactone **8** in 44.8% yield (unoptimized) by the following sequence: (1) Me_2S (MeOH/CH_2Cl_2, rt, 1 h); (2) evaporation of excess Me_2S and CH_2Cl_2; (3) H_2O_2 in the amount of 7 equiv (5 equiv $KHCO_3$, aq MeOH, rt). This alternative furan degradation method has much potential and deserves further study.

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(19) Use of acetic acid as the carbonyl oxide trap instead of methanol allows the dimethyl sulfide reduction step to be omitted, but the yield of **5** was only 78%.

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