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Novel Fragmentation Reaction of Correolide

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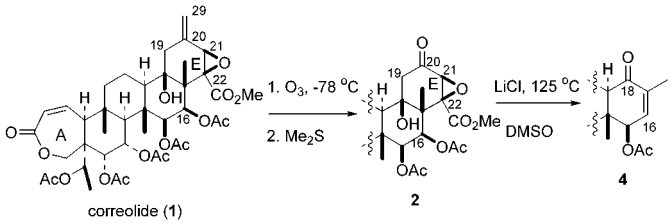
ABSTRACT



Pentacyclic triterpenoid natural product correolide (1) was converted to ketone 2 via ozonolysis. An unusual fragmentation reaction of ketone 2 with LiCl was discovered. This reaction is general among several similar substrates examined and appears to be specific for the correolide-type E-ring structure (ketone). A mechanism involving a retroaldol reaction, a nucleophilic opening of the epoxide, and a subsequent acetoxy elimination reaction was proposed.

Correolide (**1**), a pentacyclic nor-triterpenoid from *Spachea correa* is a potent and selective Kv1.3 ion channel blocker.[1] The Kv1.3 channel is a voltage-gated potassium channel that is present in human T lymphocytes and controls the T cell membrane's resting potential.[2−3] In human T cells, blocking of the Kv1.3 channels causes membrane depolarization, which prevents the increase in intracellular calcium required for T cell activation and proliferation. Blockade of the Kv1.3 ion channel represents a new mechanism for inducing immunosuppression. As part of our medicinal chemistry studies, we have been interested in the chemical and biological properties of this unusually oxygenated pentacyclic system. Herein, the initial investigation at the E-ring of the pentacycle is presented.

The E-ring of **1** has a high density of reactive groups. The six carbons that comprise the ring contain a tertiary hydroxy group, a terminal olefin, an epoxide, and a carboxymethyl group. Selective manipulation of these functionalities is further complicated by an endocyclic olefin and six additional esters in the remaining rings. The terminal olefin of **1** is selectively reduced with Wilkinson's catalyst, and ozonolysis of **1** at 0 °C is exhaustive, oxidizing both the endocyclic and exocyclic olefins.[4] The exocyclic olefin is regioselectively cleaved by reacting **1** with ozone at −78 °C and reducing the C20−C29 ozonide with methyl sulfide to afford the C20 ketone **2** in quantitative yield.[4−5] The tertiary hydroxy group of **2** is quite stable and does not eliminate under the reaction conditions.

(1) For references on triterpenes, see: (a) Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189−2206. (b) Woggon, W. D. *Hel. Chim. Acta* **1993**, *76*, 60−93. (c) Johnson, W. S.; Plummer, M. S.; Reddy, S. P.; Bartlett, W. R. *J. Am. Chem. Soc.* **1993**, *115*, 515−521. (d) Deslogchamps, P. *Pure Appl. Chem.* **1992**, *64*, 1831−1847.

(2) Goetz, M. A.; Hensens, O. D.; Zink, D. L.; Borris, R. P. Francisco, M.; Tamayo-Castillo, G.; Slaughter, R. S.; Felix, J.; Ball, R. G. *Tetrahedron Lett.* **1998**, *39*, 2895−2898.

(3) (a) Leonard, R. J.; Garcia, M. L.; Slaughter, R. S.; Reuben, J. P. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 10094−10098. (b) Felix, P. J.; Bugianesi, R. M.; Schmalhofer, W. A.; Brris, R.; Goetz, M. A.,; Hensens, O. D.; Bao, J.; Kayser, F.; Parsons, W. H.; Rupprecht, K.; Garcia, M. L.; Kaczorowski, G. J.; Slaughter, R. S. *Biochemistry* **1999**, *38*, 4922−4930. (c) Koo, G. C.; Blake, J. T.; Shah, K.; Staruch, M. J.; Dumont, F.; Wunderler, D.; Sanchez, M.; McManus, O. B.; Fischer, P.; Boltz, R. C.; Goetz, M. A.; Baker, R.; Bao, J.; Kayser, F.; Rupprecht, K. M.; Parsons, W. H.; Tong, X.; Ita, I. E.; Pivnichny, J.; Vincent, S.; Cunningham, P.; Hora, D., Jr.; Kaczorowski, G.; Springer, M. S. *Cell. Immunol.* **1999**, *197*, 99−107.

(4) Baker, R. K.; Kayser, F.; Bao, J.; Kotliar, A.; Parsons, W. H.; Rupprecht, K. M. U.S. Patent 5,874,594, 1999.

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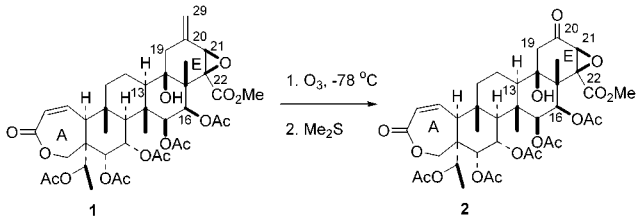
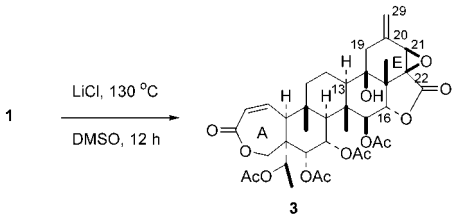
Scheme 1. Ozonolysis of Correolide (**1**)



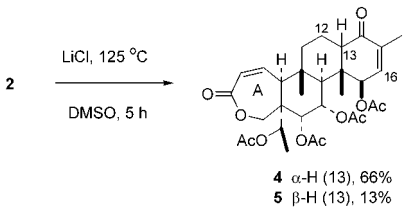
The C22 methyl ester is unique among the seven esters in **1** and should be distinguishable from the others via an S_N2-type de-esterification. Heating **1** at 130 °C with LiCl in dimethyl sulfoxide afforded a new product whose NMR and mass spectra were consistent with lactone **3**.[6] This was not unexpected since modeling suggests that the C22 carboxy group is oriented directly beneath the C16 acetoxy group and is set up for a second intramolecular S_N2 displacement at C16.

Scheme 2. Reaction of Correolide (**1**) with LiCl



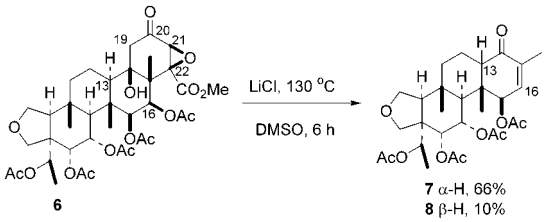
When the C20 keto analogue **2** was subjected to the same conditions, two products whose mass spectra showed a loss of 202 mass units and whose NMR spectra indicated only five ester carbonyl groups as well as an α,β-unsaturated ketone were obtained. Subsequent NMR studies confirmed that in both products, the entire E-ring and the C16 acetoxy group had been lost to afford tetracycles **4** and **5**, which were epimeric at the C13 position. The stereochemistry at C13 of epimers **4** and **5** was established through NOE experiments as well as coupling constants between H13 and H12 (H13 of **4**, 2.26 ppm (d of d, J = 12.2, 3.5 Hz); H13 of **5**, 2.66 ppm (t, J = 3.5 Hz)). This reaction was studied in detail.

Scheme 3. Reaction of **2** with LiCl



It was believed that the first step of the fragmentation process is a retro-aldol reaction, and LiCl has been known to catalyze the aldol (and therefore the retro-aldol) process.[7] The presence of LiCl is necessary, since no reaction was observed when **2** was heated at 135 °C in DMSO for 14 h without LiCl. Epimerization of **4** at C13 to form enone **5** is believed to occur after the fragmentation since the ratio of **5**:**4** increases with extended reaction time.

Scheme 4. Reaction of **6** with LiCl



Other A-ring analogues **6** and **9** that contain a C20 carbonyl group were prepared from correolide (Schemes 4 and 5).[8] Both compounds fragmented when treated under the same conditions. While fragmentation of **6** was not solvent sensitive, the yields from **9** were lower in DMSO and the best yields were obtained when DMF was used as the solvent. A small amount of diketone **12** was also isolated from the reaction of **9**. In both cases, the amount of C13 epimerization was proportional to the reaction time. Substrates **6** and **9** were selected for later studies because of their greater stability under hydrolytic conditions.

If the first step of the fragmentation is a retro-aldol reaction, it should also be induced under basic conditions. When the β-hydroxy ketone **6** was dissolved in a 1:2 mixture of saturated $NaHCO_3$ in THF, a 1:1 equilibrium mixture of diketone **13** and starting **6** resulted.[9−12] A slightly different ratio was obtained with β-hydroxy ketone **9** under the same

(5) For α,β-epoxy ketone, see: (a) Engman, L.; Stern, D. *J. Org. Chem.* **1994**, *58*, 5179−5183. (b) Urabe, H.; Sato, F. *J. Synth. Org. Chem. Jpn.* **1993**, 14−16. (c) Pegorier, L.; Petit, Y.; Mamhu, A.; Larchevegue, M. *Synthesis* **1994**, 1403−1405.

(6) For lithium halide promoted decarboxylation and demethylation, see: (a) Molander, G. A.; Siedem, C. S. *J. Org. Chem.* **1995**, *60*, 130−138. (b) Krapcho, P. A. *Synthesis* **1982**, 805−822 and 893−914. (c) Magnus, P.; Gallagher, T. *J. Chem. Soc., Chem. Comm.* **1984**, 389−390.

(7) For LiCl in aldol reaction, see: (a) Kelleher, R. G.; McKervey, M. A.; Vibuljan, P. *J. Chem. Soc., Chem. Comm.* **1980**, 486-488. (b) Antonioletti, R.; Bonadies, F.; Monteagudo, E. S.; Scettri, A. *Tetrahedron Lett.* **1991**, *32*, 5373−5374. (c) Ozaki, Y.; Kubo, A.; Kim, S.-W. *Chem. Lett.* **1993**, 993−994.

(8) (a) Compound **6** was prepared from **1** by a three-step sequence: Supporting Information. (b) Compound **9** was prepared from **1** by a four-step sequence: Supporting Information.

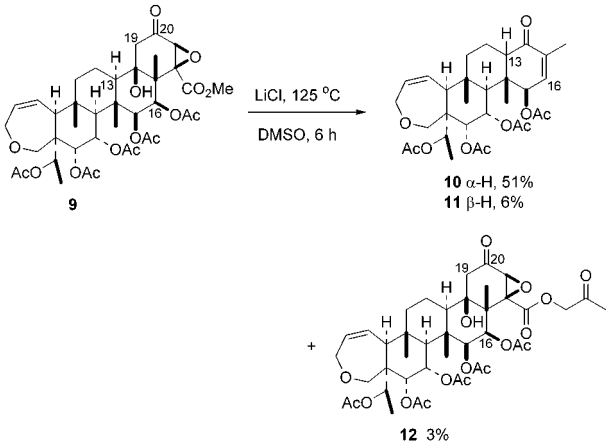
(9) Stronger bases such as LHMDS also effect this reaction as well as the subsequent fragmentation, but conversions were poor due to the other base-sensitive groups in the molecules.

(10) For intramolecular aldol condensations to form β-hydroxy ketone, see: (a) Marshall, J. A.; Fanta, W. I. *J. Org. Chem.* **1964**, *29*, 2501−2506. (b) Spencer, T. A.; Neel, H. S.; Ward, D. C.; Williamson, K. L. *J. Org. Chem.* **1966**, *31*, 434−436.

(11) For preparation of 1,5-diketones, see: (a) Le Roux, C.; Gaspard-Iloughman, H.; Dubac, J. *Bull. Soc. Chim. France* **1993**, *130*, 832−842. (b) Cohen, T.; Zhang, B.; Cherkauskas, J. P. *Tetrahedron* **1994**, *50*, 11569−11584.

(12) For aldol reaction of 1,5-diketones, see: Page, P. C.; Marchington, A. P.; Graham, L. J.; Harkin, S. A.; Wood, W. W. *Tetrahedron* **1993**, *49*, 10369−10386.

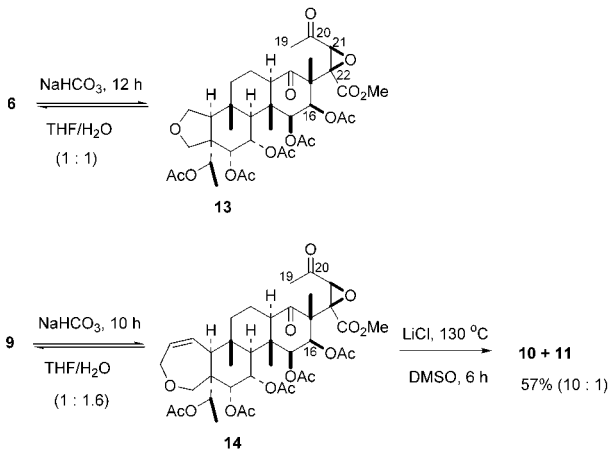
Scheme 5. Reaction of **9** with LiCl



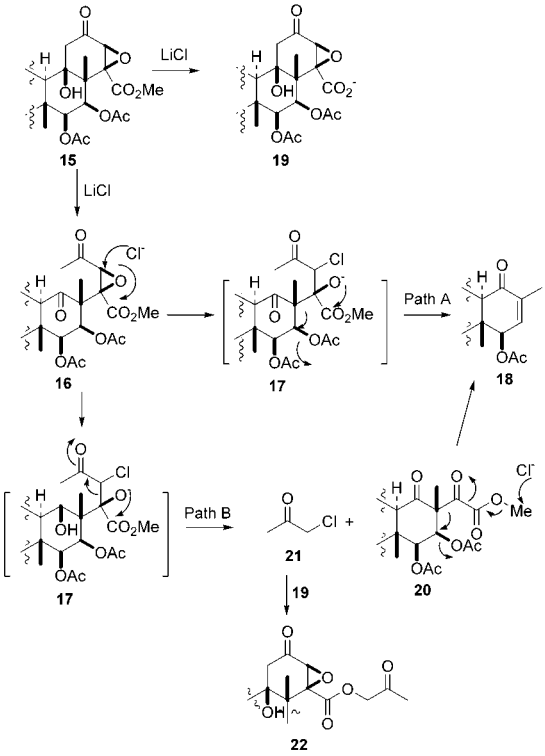
reaction conditions. The intermediacy of the diketone during formation of the des-E-ring ketone is supported by the isolation of a trace amount of des-E-ring enones from this equilibrium reaction (2% of **10** and 0.5% of **11**). Diketone **14** fragmented upon heating with LiCl in DMSO to afford a 10:1 mixture of C13 epimers **10** and **11**.

A mechanism was proposed on the basis of the above observations (Scheme 7). The first step in the fragmentation of the E-ring ketone **15** would be a retrograde aldol reaction that produces diketone **16**. Attack by chloride anion or other nucleophile at C21 of diketone **16** opens the epoxide, which then fragments along either path depicted in Scheme 7. While path A would lead to enone **18**, path B would provide α-keto

Scheme 6. Reaction of **6** and **9** with Sodium Bicarbonate



Scheme 7. Proposed Mechanism for Fragmentation of Ketones



ester **20** and chloroacetone **21**. Reaction of the carboxyl anion **19** with chloroacetone **21** would afford diketone **22** (**12** in the case of ketone **9**). Attack by chloride anion at the methyl ester of **20** and subsequent fragmentation would also provide enone **18**.

In summary, an unusual fragmentation reaction of ketone **2** was discovered. The product of this fragmentation represents a significant simplification of correolide (**1**) and opened up the possibilities of synthesizing potent Kv1.3 ion channel blockers via total synthesis. Studies toward the further elucidation of the mechanistic aspect of this reaction are currently underway.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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