Tetrahedron Letters,Vol.29,No.15,pp 1747-1750,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

LACTONE SYNTHESIS VIA DYOTROPIC REARRANGEMENT. STEREOSPECIFIC CONSTRUCTION OF FUSED BUTYROLACTONES WITH THREE CONTIGUOUS ASYMMETRIC CENTERS

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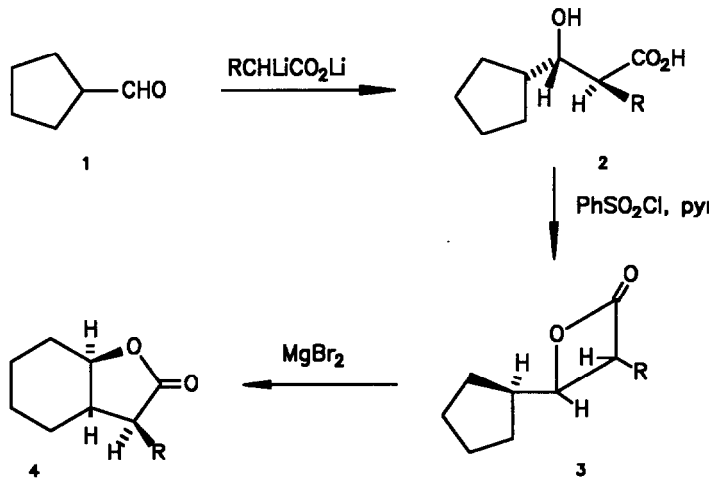
Substituted trans-fused cyclohexano butyrolactones are accessible via dyotropic rearrangement of ß-lactones, wherein all three adjacent chiral centers are simultaneously fixed.

Butyrolactones fused to a cycloalkane ring comprise a widespread structural subunit throughout naturally-occurring molecules,[1] being found both cis- and trans-fused to either six- or seven-membered carbocyclic rings. Many synthetic approaches to fused lactones have been recorded,[2] usually relying upon stereoselective functional group manipulations to construct the ring fusion in the desired sense. One of the more synthetically challenging lactone configurations is trans fusion to a cyclohexane ring (a trans hexahydro-2(3H)-benzofuranone), since it is energetically disfavored relative to its cis isomer.[3] The situation is further complicated if a stereochemically-defined substituent is desired on the lactone ring, such as exists in sesquiterpene lactones such as santonin and artemisin.[4] We wish to report a conceptually unique approach to such systems which utilizes a dyotropic rearrangement as the key step and simultaneously establishes the relative configuration of all three contiguous chiral centers.

We have recently recognized the dyotropic rearrangement as a useful mechanism for the stereospecific synthesis of various lactone classes, including monocyclic[5] and spiro[6] butyrolactones. In the preparation of the latter, trans 3-substituted 4-cyclohexyl ß-lactones were found to rearrange with the lactone ring expansion accompanied solely by hydrogen migration. This is a general phenomenon, provided that the requisite anticoplanar geometry of the migrating bonds can be achieved. However, it is a primary goal of our program to develop conditions wherein carbon migration would provide the preferred reaction pathway. Since expansion from a five- to six-membered ring is exothermic (ca. 6 kcal/mol),[7] as opposed to the situation for the next higher homolog, we reasoned that carbon migration might be energetically favored to the point of overcoming the proclivity for hydrogen migration

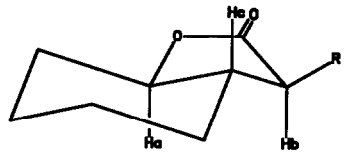
observed in all other cases thus far. We therefore prepared molecules bearing a cyclopentyl substituent in place of the cyclohexyl ring, as outlined below, and were gratified to discover that not only is carbocyclic ring expansion the only observed reaction, but that the inherent stereospecificity of the dyotropic rearrangement enables the simultaneous fixation of all three contiguous asymmetric centers in the same relative configuration as that which occurs in many natural products. α-Santonin and α-artemisin, for example, possess the same trans,trans configuration as in **4**, but to date have been synthesized only via stereoselective techniques which produce significant amounts of undesired stereoisomers.[8]



The reaction sequence, which proceeds in greater than 45% yield overall, is operationally quite straightforward. Cyclopentanecarboxaldehyde (1)[9] was treated with phenyl- or phenoxyacetic acid dianion,[10] and the resulting threo[11] ß-hydroxy acid **2** was purified via recrystallization from hexane. This protocol proved to be essential to remove small amounts of the erythro diastereomer, which, if carried through the remainder of the sequence, damages the isomeric purity of the final product. Cyclization to the trans ß-lactone **3**[12] was accomplished in high yield by treatment with benzenesulfonyl chloride in pyridine;[13] filtration through silica gel with dichloromethane as eluent provided very pure material. Rearrangement to the trans,trans butyrolactone **4** was effected by brief exposure of the ß-lactone to magnesium bromide etherate in diethyl ether at room temperature. These products exhibited spectral properties and gave combustion analyses in excellent agreement with their

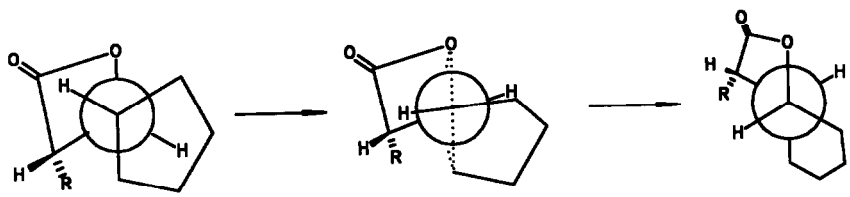
structures.[14]

The trans,trans stereochemistry was surmised from two significant measurements via 360 MHz NMR spectroscopy. Ha appeared as a triplet of



doublets centered at 3.901 ppm (R = PhO), which has been demonstrated to be indicative of a trans ring fusion regardless of substituent patterns.[15] Hb exhibited a doublet with coupling constants of sufficient magnitude (R = PhO, J = 11.60; R = Ph, J = 12.91) to confirm the trans relationship of Hb and Hc.[16] The NMR spectra were exceptionally clean and uncontaminated with isomeric reaction products.

The stereospecificity of the rearrangement lies in its concerted nature, and is addressed in the Figure. The trans ß-lactone 3 is portrayed in the



lowest energy conformation in which a carbon-carbon bond in the cyclopentane ring is aligned with the lactone carbon-oxygen bond; this places the methine protons anti to one another. This trans relationship is maintained during the simultaneous sigma bond migrations, as is the relative configuration of the R substituent and the adjacent center established during the initial condensation reaction.

We believe this to be the first example of a stereospecific butyrolactone synthesis wherein three contiguous asymmetric centers are simultaneously fixed in a predictable relative configuration identical to that found in naturally occurring molecules. Extension of the method to more complex systems is under active investigation.

Acknowledgement: We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. The Dow Chemical Company Foundation is acknowledged for partial summer support for W.J.D. NMR data were acquired with the assistance of the Molecular Spectroscopy Laboratory of the University of Illinois at Urbana-Champaign.

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14. R = Ph: mp 67-70°; IR (KBr) 2948, 2863, 1777, 1168, 1139 cm.-1; NMR ($CDCl_3$) 7.39-7.21 (m, 5H, ArH), 3.92 (m, 1H, CHOC=O), 3.44 (d, J=12.91Hz, 1H, PhCH), 2.17-1.29 (m, 9H, aliphatic H); TLC (dichloromethane) Rf 0.43. R = PhO: mp 110-112°; IR (KBr) 2980, 2834, 1785, 1596, 1589 cm.-1; NMR ($CDCl_3$) 7.29-7.05 (m, 5H, ArH), 4.73 (d, J=11.60Hz, 1H, PhOCH), 3.90 (m, 1H, CHOC=O), 2.30-1.32 (m, 9H, aliphatic H); TLC (dichloromethane) Rf 0.46.
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(Received in USA 28 December 1987)