Tetrahedron Letters,Vol.25,No.1,pp 19 - 22,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain 

# A UNIFIED APPROACH TO PROSTANOID AND CORTICOSTEROID SYNTHONS

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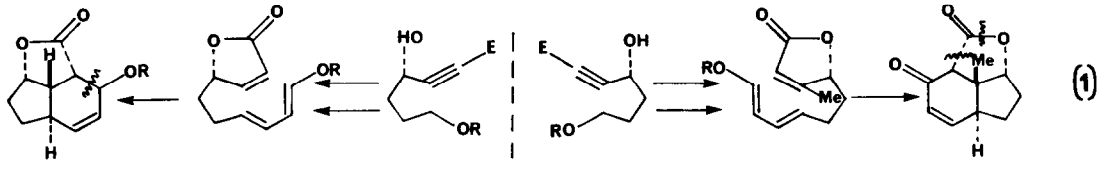
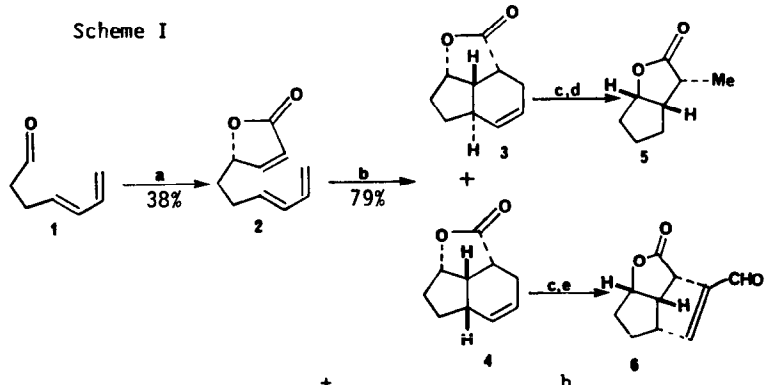
Abstract: Synthons for 11-deoxyprostanoids and 11-ketosteroids are available via intramolecular Diels-Alder reactions between oxygenated dienes and attached butenolides.

Because of their biological significance, scarcity, and structural diversity, the prostanoid and steroid hormonal agents have held the attention of synthetic chemists for many years.[1] Reported herein are studies directed at a unified approach to the synthesis of both classes of compounds. The general strategy is based upon the use of the intramolecular Diels-Alder cycloaddition,[2] as indicated in eq 1. It was anticipated that the rigid butenolide would effectively transmit dienophile orientation requirements through the tether to the diene, thus favoring the formation of trans-fused hydrindene units as synthons for 11-deoxyprostaglandins and 11-ketosteroids.[3]




The first requirements were to demonstrate that the butenolide unit would serve as an adequate Diels-Alder dienophile and to probe the exo/endo transition state orientation in an unadorned substrate. As shown in Scheme I,[4] (E)-4,6-heptadien-1-al (1)[5] was converted to the butenolide 2 in 38% yield by the method of Uda.[6] Thermolysis of 2 in toluene at 180°C (sealed tube, methylene blue, 26 h) gave in 79% yield a mixture of the tricyclic lactones 3 and 4 in a ratio of 1.08:1. The assignments as trans- and cis-fused hydrindenes, respectively, were indicated by comparing the C=C stretching frequencies in the IR spectra.[7] More convincing evidence

Scheme I



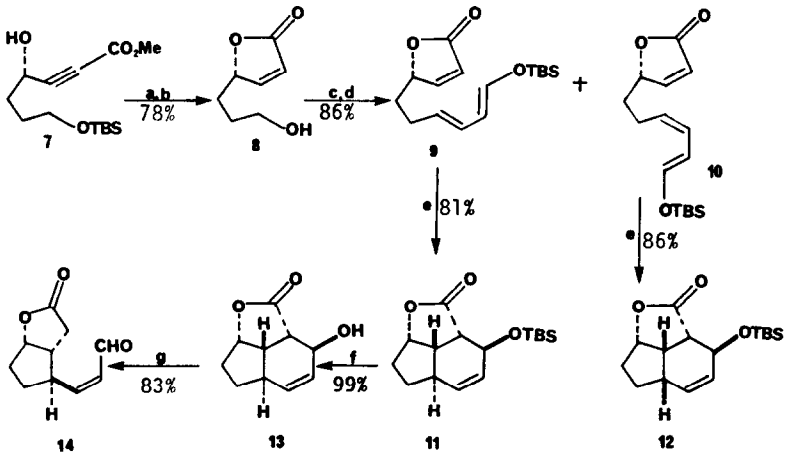

[a]$PhS(O)CHLiCH_2CO_2Li$, THF, -78°C; $H_3O^+$; $PhCH_3$, reflux. [b]$PhCH_3$, methylene blue, 180°C, 26 h. [c]$OsO_4$, $NaIO_4$, $THF/H_2O$ (1:1), 25°C, 20 min. [d]$(Ph_3P)_3RhCl$, $PhCH_3$, reflux, 18 h. [e]$SiO_2$ chromatography or $(PhCH_2)_2NH_2OCOCF_3$, THF, 25°C.

was obtained through the chemical correlations shown. The cyclohexene unit in 3 was cleaved [$OsO_4$, $NaIO_4$, THF/$H_2O$ (1:1), 25°C, 20 min][8] to give a stable dialdehyde which, upon bisdecarbonylation [$(PH_3P)_3RhCl$, $PhCH_3$, reflux, 18 h],[9] gave the known bicyclic lactone 5.[10] Cleavage of the cyclohexene unit in 4 in the same manner afforded a relatively labile dialdehyde which closed to the tricyclic enal 6 (mp 131°C) upon silica gel chromatography or upon treatment with DATA[11] in THF.

In an attempt to improve upon the diastereoselectivity of the cycloaddition and to provide a more functionalized tricyclic for further elaboration, we turned to oxygenated dienes as shown in Scheme II.[4] Semihydrogenation [$H_2$ (1 atm), Lindlar's catalyst, EtOAc, 25°C] of the acetylenic ester 7[12] followed by acid-catalyzed lactonization and concomitant cleavage of the t-butyldimethylsilyl (TBS) ether gave the butenolide 8 in 78% overall yield. Oxidation of 8 to the aldehyde with PDC/$CH_2Cl_2$[13] and Wittig olefination[14] in toluene at -20°C gave the (E,E)- and (E,Z)-dienes 9 and 10 (~ 1:1, 86%). These were separated chromatographically and were thermolized individually. With these oxygenated dienes the Diels-Alder reaction proved to be stereospecific, in that 9 gave only the trans-fused hydrindene 11 (81%, mp 91-92°C) upon thermolysis at 230°C in toluene (sealed tube, methylene blue, 72 h), while the E,Z-diene 10 gave only the cis-fused product 12 (86%, mp 61-62°C) under the same conditions. These results imply a strong preference for the exo orientation of the butenolide in the cycloaddition transition state.

The tricyclic lactone 11 was further manipulated to test the retrograde Claisen condensation suggested in eq. 1 for the scission of the six-membered carbocycle. Hydrolysis of the TBS ether (1N $H_2SO_4$/THF, 25°C) gave the allylic alcohol 13 (99%, mp 47-48°C). Addition of 13 to a suspension of KH in THF at 0°C followed by slow warming to ambient temperature and quenching with t-BuOH and HOAc gave the enal 14 as a mixture of E- and Z-isomers in 83% yield. Thus the Diels-Alder/retro-Claisen condensation sequence provided access to a synthon suitable for elaboration into 11-deoxyprostanoids.

Scheme II




[a]$H_2$(1 atm), Lindlar's cat., EtOAc, 25°C. [b]p-TsOH, 1N $H_2SO_4$, THF, 25°C, 30 min. [c]PDC, $CH_2Cl_2$, 25°C, 24 h. [d]$Ph_3PCHCH{=}CHOTBS$, $PhCH_3$, -20°C, 1 min. [e]$PhCH_3$, methylene blue, 230°C, 72 h. [f]1N $H_2SO_4$, THF, 25°C. [g]KH, THF, 0→25°C; t-BuOH, HOAc.

It was felt that, with some modification, such a Diels-Alder route to functionalized hydrindenes could also be applied to the synthesis of corticosteroid synthons. The realization of this goal is outlined in Scheme III.[4] Conversion of the propargylic alcohol 7[12] to the corresponding TBS ether[15] was followed by treatment with lithium dimethylcuprate in THF (-78°, 3h; MeOH, -78°C)[16] to give the trisubstituted olefin 15 in 93% yield. Simultaneous hydrolysis of both TBS ether groups in 15 [40% aq HF/$CH_3CN$ (5:95)] was accompanied by lactonization. Oxidation (PCC, $CH_2Cl_2$, Celite, 25°C)[17] gave the aldehydic butenolide 16 in 80% overall yield. Wittig olefination[14] gave a mixture (~ 1:1, 79%) of the E,E- and E,Z-dienes with gross structure 17. Thermolysis of this mixture in toluene at 220°C(sealed tube, methylene blue, 36 h) gave the trans-fused hydrindene 18 (29%, mp 74-74.5°C), the cis-fused hydrindene 19 (33%, mp 54°C), and recovered 17 (20%). Based upon the assumption that the ratio of trans- and cis-fused tricyclic products 18 and 19 reflected the mixture of diene isomers 17, this result confirmed the feasibility of this approach. The methyl substituent in the β-position of the butenolide dienophile did not offer serious resistance to the cycloaddition.

The trans-fused hydrindene 18 was converted to the hydrindenone 20 (96% mp 114-115°C) by hydrolysis of the TBS ether [40% aq HF/$CH_3CN$ (5:95)] followed by Jones oxidation. In 20 the angular methyl group effectively shields the β-face of the enone moiety. Thus, a Sakurai allylation[18] ($CH_2$=$CHCH_2SiMe_3$, $TiCl_4$, $CH_2Cl_2$, -78°C, 6h) proceeded cleanly to give the hydrindanone 21 (85%, mp 84°C), in which the incipient C(8) center (steroid numbering) was established with the proper relative configuration. Hydrolysis of the lactone [NaOH, EtOH/$H_2O$ (1:1), reflux, 4h] with concomitant decarboxylation gave the corticosteroid synthon 22 in quantitative yield.

In order to confirm the relative stereochemical assignments in Scheme III, a single crystal of 21 was subjected to x-ray diffraction analysis.[19] The ORTEP[20] drawing shown in Figure I reveals the trans-fusion of the nascent steroid CD ring system, the α-orientation of the C(8) allyl substituent, and the stereochemistry of the γ-lactone bridging the C(12) and C(17) sites.

Scheme III

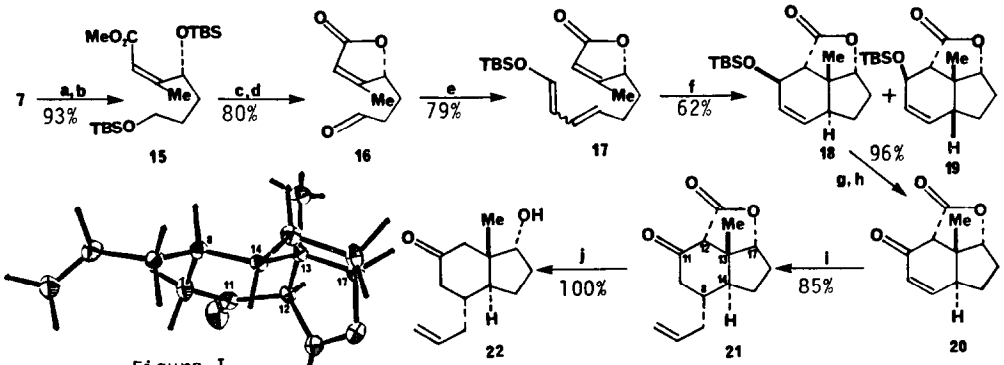



Figure I

[a] TBSCl, imidazole, DMF, 25°C, 30 min. [b] $LiMe_2Cu$, THF, -78°C, 3 h, MeOH, -78°C. [c] 40% aq HF, $CH_3CN$, 25°C, 30 min. [d] PCC, $CH_2Cl_2$, Celite, 25°C. [e] $Ph_3PCHCH$=CHOTBS, THF, -78°C; aq $NH_4Cl$, 0°C. [f] $PhCH_3$, methylene blue, 220°C, 36 h. [g] 40% aq HF, $CH_3CN$, 25°C, 30 min. [h] Jones oxidation, 0°C [i] $CH_2$=$CHCH_2SiMe_3$, $TiCl_4$ $CH_2Cl_2$, -78°C, 6h; $H_2O$, -20°C. [j] NaOH, $H_2O$/EtOH (1:1), reflux, 4 h.

Acknowledgement. We gratefully acknowledge the National Institutes of Health (GM 28321) for generously supporting this research. High-field NMR spectra were obtained through the NSF Regional NMR Center at the University of South Carolina (CHE 78-18723).

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(Received in USA 11 October 1983)