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Tandem Cyclopropylcarbinyl/Oxiranylcarbinyl Radical Rearrangements: An Entry into the Prostaglandin B_1 Series

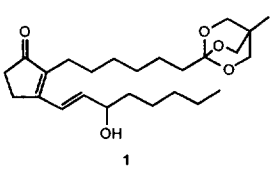
Frederick E. Ziegler* and Anders K. Petersen

Sterling Chemistry Laboratory ,Yale University, New Haven, CT 06520-8107 USA

Abstract: A tandem radical fragmentation of a cyclopropylcarbinyl/oxiranylcarbinyl system leads to the PGB_1 series of prostaglandins. Control of cyclopropane bond fragmentation as a function of C_2 substitution in bicyclo[3.1.0]hexanylcarbinyl radicals is presented.

Early studies on the synthesis of prostaglandins employed base-initiated opening of cyclopropyl oxiranes as a route to the B_1 series[1,2] and solvolysis as an entry to the F_1 series.[3] The use of vinylcyclopropanes by other investigators led to successful pathways to the $F_{2\alpha}$ series[2,4] and A_1 and E_2 series.[5,6] Our recent study on the tandem radical fragmentation of cyclopropyl oxiranes[7] prompted us to explore the utility of this reaction in the synthesis of prostaglandin derivatives. In this Letter we provide the details of the synthesis of PGB_1 orthoester **1**.

Cyclopropane **2** was prepared by intramolecular α-diazo-β-keto ester addition as described for the methyl[4] and ethyl esters[5] (Scheme 1). Selective reduction of β-keto ester **2** via the TIPS enol ether[7] afforded cleanly ketol **3** in 71% yield. At this juncture both oxidation of the alcohol to an aldehyde and epoxidation of the double bond were required. To this end, ketol **3** was oxidized with Dess-Martin periodinane.[8] No aldehyde **4** was observed but rather a single dihydrooxepin **5**, which was formed via a retro-Claisen rearrangement, was isolated in 87% yield. The enhanced facility with which these rearrangements occur when two carbonyl groups are substituted geminally on the cyclopropane ring has been reported by Boeckman.[9-11] The assignment of stereochemistry of oxepin **5** was based upon the syn-boat transition state for the rearrangement of cis-1,2-divinylcyclopropanes.[12]



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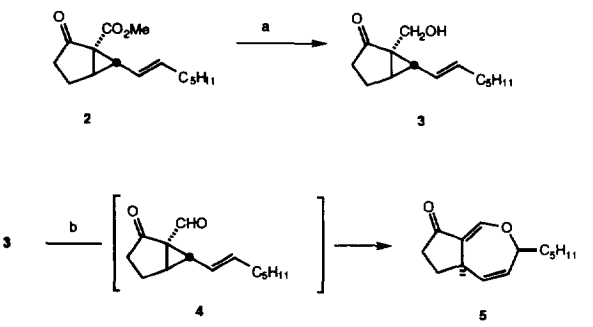
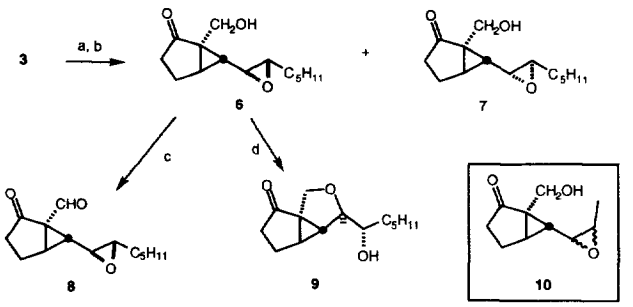
Efforts to attain stereoselective epoxidation of the double bond of ketol **3** through participation of the hydroxyl function proved unrewarding. The TIPS ether of **3**, which provided little facial discrimination, gave a 3:2 mixture (α:β) of epoxides upon oxidation with m-CPBA. Oxidation of ketol **3** with trifluoroperoxyacetic acid[7,13] furnished a 3:2 mixture (β:α) of epoxy trifluoroacetates, which were deprotected in methanol to the epoxy ketols **6** and **7** in 81% yield (Scheme 2). Separation of the alcohols by radial chromatography on silica gel caused partial (18%) conversion of epoxide **6** to tetrahydrofuran **9**. The stereochemical assignments of **6** and **7** were made at this juncture by comparison of their ^1H NMR spectra with the known four stereoisomers of epoxide **10**.[7] Oxidation of ketol **6** with Dess-Martin periodinane in the presence of pyridine readily provided keto aldehyde **8** (91%). The separation of ketols **6** and **7** was conducted to minimize stereoisomers in the synthetic sequence. However, a mixture of **6** and **7** could have been employed because the final target **1** has but one stereogenic center.

Scheme 1



a) one pot procedure; i) LDA (1.4 equiv), THF, -42 °C, 15 min; ii) TIPSOTf, -42 °C, 15 min;
iii) DIBALH (3 equiv), -42 °C, 45 min; iv) 1:1 AcOH/H_2O, 25 °C, 7 h; b) Dess-Martin periodinane, 0 °C, 10 min.

Scheme 2

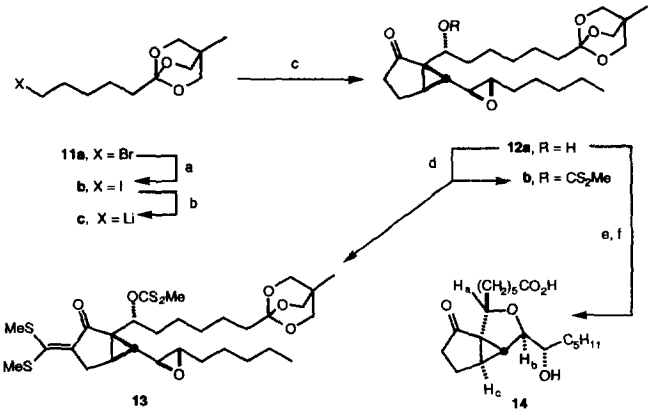


a) urea·H_2O_2/TFAA/Na_2HPO_4, 25 °C, 30 min; b) MeOH, 3Å mol. sieves, 25 °C, 75 min;
c) Dess-Martin periodinane, CH_2Cl_2/pyr , 0 --> 25 °C, 35 min; d) silica gel, 10% EtOAc/hexane.

The known[15,16] bromide **11a** (Scheme 3) was converted into the iodide which was, in turn, metallated as prescribed by Bailey[17]and Negishi.[18] Addition of the organolithium reagent **11c** to keto aldehyde **8** led to the isolation of a modest yield (21%) of a single ketol product having the stereochemistry depicted in structure **12a**. Alternative organometallic reagents (RMgX, RZnI, $RCeCl_2$) failed to improve the yield. The stereochemistry of this ketol product was determined in the same fashion as was the stereochemistry of tetrahydrofuran **9**. Treatment of **12a** with TFA formed the tetrahydrofuran **14**, which showed mutual NOE enhancements among the protons H_a, H_b, and H_c. Ketol **12a** was readily converted into its xanthate **12b** in 60% yield along with the formation of **13** (9%), a product of carbon thioacylation.

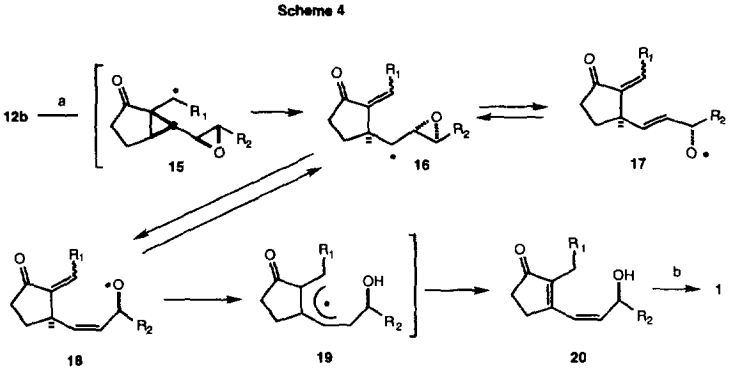
PGB_1 orthoester **1** was formed in 55% yield from xanthate **12b** by an intricate radical cascade. The mechanism of the tandem fragmentation (Scheme 4) follows along lines described previously for simpler systems.[7] Xanthate **12b** undergoes Barton-McCombie reduction[19] to the secondary cyclopropylcarbinyl radical, which preferentially ruptures the cyclopropane bond overlapping with the carbonyl group to provide the oxiranylcarbinyl radical **16**. This radical is in rapid equilibrium with the (*E*)- and (*Z*)-allyloxyl radicals **17** and **18**, respectively.[14]

Scheme 3



a) NaI, acetone, 25 °C, 4 h; b) *t*-BuLi, Et_2O/pentane, -78 °C (15 min), 25 °C (1 h); c) **8**, THF, -78 °C, inverse add'n, 25 min; d) i) LDA, THF, 0 °C ii) CS_2 iii) MeI; e) TFA (cat.), CH_2Cl_2, 25 °C, 15 h; f) LiOH, 75% aq. THF, 25 °C, 2.5 h.

Scheme 4



a) Bu_3SnH (2 equiv), AIBN (1 equiv), toluene, 75 °C, 2 h; b) stannyl Lewis acids.

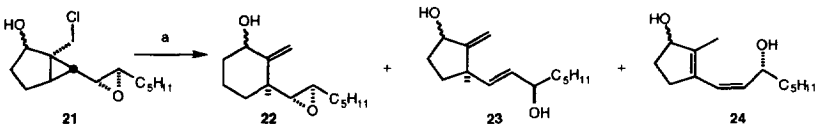
Intramolecular hydrogen atom abstraction in **18** prevails over bimolecular trapping of **17** at low donor concentration (< 0.05 M). The initially formed (*Z*)-dienone **20** isomerized to the (*E*)-isomer **1** in the presence of tin salts.

Overlap between the π-bond of the carbonyl group with the peripheral cyclopropane bond controls the kinetic cleavage of cyclopropylcarbinyl radical **15** to oxiranylcarbinyl radical **16**. When the carbonyl group is reduced to an alcohol and the xanthate is replaced by a chlorine atom, kinetic cleavage of the internal cyclopropane bond occurs (Scheme 5). Substitution of chlorine for the xanthate moiety prevents premature reduction of the xanthate prior to formation of the cyclopropylcarbinyl radical at high Bu_3SnH concentration. Reduction of chloride **21** in neat Bu_3SnH (3.72 M) gave methylenecyclohexanol **22** (54%) and a mixture of (*E*)-allylic alcohol **23** (13%) and (*Z*)-dienediol **24** (5%). In 0.08 M Bu_3SnH, the yield of **22** was 38% while **23** and **24** were formed in trace amounts. These data strongly suggest that, in the absence of the carbonyl group, zero bridge cleavage of the [3.1.0]

system is kinetically preferred.[20] Noteworthy is the appearance of 13% of (*E*)-allylic alcohol **23** in neat Bu_3SnH, the first time that an (*E*)-allylic alcohol has been produced in these systems.

Scheme 5

(β/α alcohols, 90/10)



a) Bu_3SnH, 3.72 M (neat), AIBN (cat.), 90 °C, 1 h.

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(20) There is the possibility that the selectivity is not caused by the π-bond overlap of the carbonyl group but rather by strain difference associated with sp^2 vs. sp^3 hybridization in the carbonyl and carbinol, respectively.

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