STEREOSPECIFIC 1,4-ADDITION REACTION OF SULFINYLALLYL ANION: SYNTHESIS OF (±)-PENTALENOLACTONE E METHYL ESTER

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Summary: Stereospecific 1,4-Addition reaction of lithiated sulfinylallyl anion and enone 2 provided the corresponding $1,4-\gamma$ -adduct, 7. In seven steps, 7 was converted into octahydro-2-methoxy-8,8-dimethylpentalenol[1,6a-c]pyran-5-(6<u>H</u>)-one (9) whose conversion into pentalenolactone E methyl ester (1) has been previously reported.

The stereospecific 1,4-addition reactions of sulfinylallyl anions with cyclic enones constitute a mild and versatile method for annulation.¹ In the continuation of the synthesis of the pentalenane family utilizing this addition reaction,^{1b} the synthesis of pentalenolactone E methyl ester (1)^{2,3} was studied. The key step in the synthesis is the facile lactolization reaction of a ς -silyloxy α,β -unsaturated sulfide with ozone for the construction of the C-ring.

 $2 - [(\underline{t}-Butyldimethylsilyloxy)methyl] - 7,7-dimethylbicyclo[3.3.0]oct-2-en-3-one (2)⁴ was$ easily prepared in a three-stage reaction sequence from readily available 4,4-dimethyl-1-hepten-6-yne (3):^{1b} (i) hydroxymethylation of 3 with 1.1 equiv of <u>n</u>-BuLi in THF (10 mL/g) at -78 °Cfor 1 h followed by 1.1 equiv of paraformaldehyde in hexamethylphosphoramide (HMPA; 5 equiv) and $THF at -20 °C for 10 min, and 25 °C for 1 h (90% yield); (ii) silylation with 1.5 equiv of <math>\underline{t}$ butyldimethylsilyl chloride-3 equiv of Et₃N-0.2 equiv of 4-dimethylaminopyridine (DMAP) in CH₂Cl₂ (10 mL/g) at 25 °C for 12 h (89% yield); and (iii) cobalt carbonyl promoted cocyclization with 1 equiv of Co₂(CO)₈ in heptane (11 mL/g) under CO atmosphere^{1b,5} in a sealed tube at 25 °C for 24 h, and 80 °C for 48 h (65% yield).

Treatment of racemic <u>p</u>-tolyl allyl sulfoxide (6) with 1.1 equiv of lithium diisopropylamide (LDA) in THF at -78 °C for 1 h followed by 0.9 equiv of enone 2 in THF at -78 °C for 10 min provided 60% yield of the 1,4- γ -adduct, 7 and 25% yield of 8 (mp 98~99 °C). Enone 8 resulted from the rapid elimination of <u>t</u>-butyldimethylsilyloxy ion from the initially formed enolate ion

adduct. Together with the sharp mp, 1 H and 13 C NMR spectra support the proposed single diastereomeric structure of $m{8}$. The relative stereochemistry at the sulfur atom, C-1 and C-5 of 8 was proven by X-ray diffraction of a single crystal.^{1d} This proof, in turn, provides firm evidence of the stereochemical course followed in addition reactions of sulfinylallyl anions with cyclic enones. Ketone 7 can be converted to enone ${f 8}$ by brief treatment with base (e.g., KOH in MeOH). 1 H and 13 C NMR spectra of 7 indicate it is a single isomer, in which the C-2 silyloxymethyl group is oriented on the exo face of the bicyclo[3.3.0]octanone ring. This stereochemistry is proven from the transformation of 7 to the known δ -lactol methyl ether 9 (vide infra).^{3a,c} Reduction of ketone 7 with 2 equiv of NaBH, in MeOH (10 mL/g) at -10 °C for 2 h gave 92% yield of exo-alcohol 10 and 4% yield of endo-alcohol 11. The stereochemistry at C-3 of 10 was assigned on the assumption that sodium borohydride attacked the C-3 carbonyl group from the opposite face of the C-2 \underline{r} -butyldimethylsilyloxymethyl group. Acetylation of exoalcohol 10 with 1.5 equiv of acetyl chloride and 5 equiv of pyridine in CH_2Cl_2 (20 mL/g) at 0 °C for 2 h produced 50% yield of sulfide 13 and 42% yield of sulfoxide 12. Apparently, acetylation of the C-3 OH group and reduction of sulfoxide group took place under these mild and basic conditions. This mild reduction of sulfoxides with acetyl chloride-pyridine has not been previously reported.⁶ Sulfoxide 12 was converted to sulfide 13 with either zinc-AcOH 1a or the above acetyl chloride-pyridine reagent (90% yield).

Ozonolysis of sulfide 13 with 4 equiv of ozone in CH_2Cl_2 and MeOH at -78 °C for 1 h, followed by addition of excess dimethyl sulfide afforded epimeric δ -lactol methyl ether 14 (51% yield) and δ -lactone 15 (30% yield), the latter resulting from the oxidation of 14 by ozone.⁷ The <u>t</u>-butyldimethylsilyl ether protecting group was lost during the ozone treatment,⁸ and the resulting hydroxy aldehyde (17) underwent lactolization and acetal formation. Since acetal 14 was the desired intermediate, it was obtained in higher yield (83%) by a two-stage reaction sequence from 13: (i) ozonolysis with 1.5 equiv of ozone in CH_2Cl_2 and MeOH at -78 °C (90% yield); and (ii) desilylation followed by lactolization of the resulting aldehyde (16) with 10 equiv of 48% HF in MeOH at 25 °C for 1 h (92% yield). Acetate 14 was transformed into ketones 9 by the sequence: (i) deacetylation with 1 equiv of $K_2\text{CO}_3$ in MeOH at 25 °C for 1 h (96% yield); and (ii) oxidation of the resulting alcohol (18) with 2 equiv of pyridinium chlorochromate in CH_2Cl_2 at 25 °C for 1 h (92% yield).⁹ IR, ¹H and ¹³C NMR, and mass spectra of epimeric ketones





~R





7



8

6





10 : X = O, $R^{1} = OH$, $R^{2} = H$ 11 : X = O, $R^{1} = H$, $R^{2} = OH$ 12 : X = O, $R^{1} = OAc$, $R^{2} = H$ 13 : $X = :, R^{1} = OAc, R^{2} = H$







9 were identical to those reported by Cane and Thomas.^{3c} Conversion of ketones **9** into pentalenolactone E methyl ester (1) has already been demonstrated by other investigators; 3a,c thus, the formal synthesis of **1** is now complete.

In summary, the use of the 1,4-addition reactions of sulfinylallyl anions and cyclic enones as a strategy for the elaboration of functionalized polycyclic ring system has been explored. The reduction of sulfoxides to sulfides under mild conditions, AcCl-pyridine-0 °C, and rapid lactol formation involving enol thioether and <u>t</u>-butyldimethylsilyl ether moieties with ozone found in the context should be applicable to other syntheses.

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