Pergamon

Tetrahedron Letters, Vol. 35, No. 37, pp. 6795-6798, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

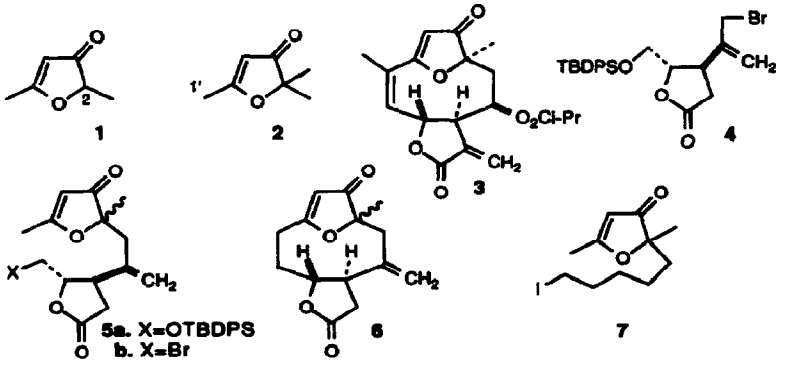
0040-4039(94)01430-2

The Synthesis of 11-Oxabicyclo[6.2.1]undecenone Derivatives[1]

Drury Caine* and Mark E. Arant
Department of Chemistry, University of Alabama
Tuscaloosa, Alabama 35487, USA

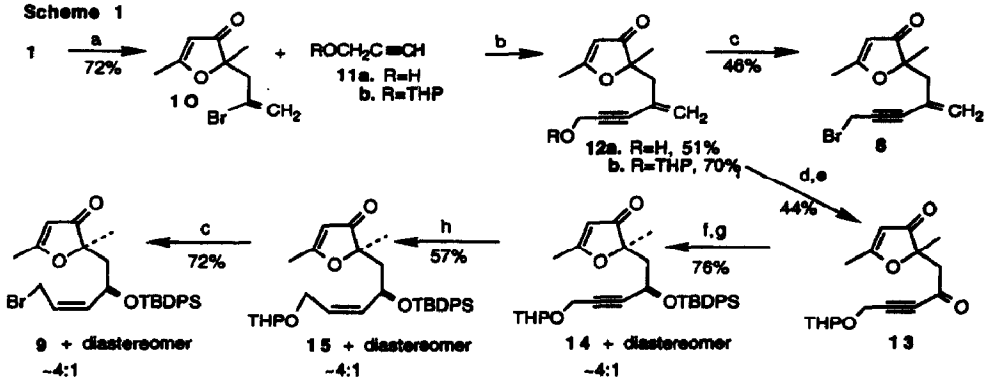
Abstract: 11-Oxabicyclo[6.2.1]undecenone derivatives **16** and **17** were synthesized via cycloalkylation of appropriately substituted monocyclic 3(2H)-furanone derivatives.

Smith and coworkers[2] have demonstrated that 2,5-disubstituted 3(2H)-furanones such as **1** undergo intermolecular alkylation at C-2 via their cross-conjugated dienolate intermediates and that the corresponding 2,2,5-trisubstituted systems such as **2** undergo intermolecular alkylation at C-1′, i.e., γ-alkylation, via their linearly conjugated dienolate intermediates. These results suggested that alkylation of furanone **1** at C-2 with a 1,5-disubstituted alkylating agent, conversion of the ω-substituent on the five-carbon side chain into a leaving group, and cycloalkylation at C-1′ would yield a 11-oxabicyclo[6.2.1]undecenone system of the type found in the A/B ring of the heliangolide sesquiterpenes,[3] e.g., ciliarin (**3**).[4] In the hope of obtaining an advanced precursor to **3**, furanone **1** was alkylated with the bromo lactone **4**[5] and the t-butyldiphenylsilyl (TBDPS)-protected hydroxyl groups of the diastereomeric mixture **5a** were converted into the corresponding bromides **5b**.[6] However, all attempts to generate the tricyclo furanone lactone **6** by base-induced cycloalkylation of **5b** failed.[6] Although the products of these reactions were not fully characterized, spectroscopic evidence indicated that intermolecular alkylation involving the lactone enolate was the major reaction pathway.[6] Also, attempted cycloalkylation of the simple ω-iodopentyl-3(2H)-furanone **7** failed.[6] In this case, the terminal alkene resulting from E-2 elimination of the iodine was the major reaction product.



Examinations of models of compounds **5b** and **7** indicated that transannular interactions involving the furanone ring and the hydrogen atoms on the sp^3 hybridized carbons of the side chains could be responsible for the failure of the desired cycloalkylation reaction. However, it appeared that if the five-carbon side chain contained a triple or a double bond adjacent to the ω-carbon atom such interactions would be significantly reduced.[7] Furthermore, in such systems, the propargylic or allylic leaving groups would be expected to be more reactive toward intramolecular S_N2 displacement than the corresponding saturated systems and the possibility of E-2 elimination would not exist. Therefore, with the objective of synthesizing 11-oxabicyclo[6.2.1]undecane derivatives with functionality suitable for possible elaboration of the γ-acyloxy α-methylene lactone systems of natural products such as **3**, the C-2 substituted 3(2H)-furanone derivatives **8** and **9** were synthesized as shown in Scheme 1.

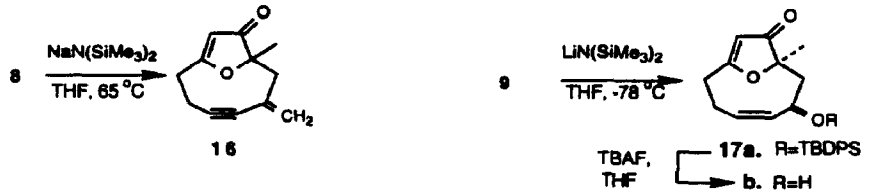
Scheme 1



a. $BrCH_2C(Br)=CH_2$, LDA, THF, -78 → 25 °C; b. CuI, $Pd(PPh)_4$, n-$BuNH_2$, PhH; c. CBr_4, PPh_3, CH_2Cl_2; d. cat. amt. OsO_4, MNO, THF-H_2O; e. $NaIO_4$, dioxane-H_2O; f. $NaBH_4$, $CeCl_3$, MeOH-H_2O; g. TBDPSCl, imidazole, CH_2Cl_2; h. H_2, $Pd/BaSO_4$, quinoline, MeOH.

Alkylation of the furanone **1** with 1,2-dibromopropene via the lithium dienolate[2] gave the bromo furanone **10**.[8] Coupling of the vinyl bromide with propargyl alcohol using the Pd^0-CuI method of Kende and Smith[9] gave the enyne alcohol **12a**[8] (51% yield) which was converted into the bromo enyne **8**[8] with CBr_4-PPh_3.[10] The cyclalkylation reactions were carried out by the slow addition of dilute solutions of **8** in THF to solutions of lithium or sodium hexamethyldisilazane in THF at temperatures ranging from -78 °C to 65 °C. The oxabicyclo compound **16** resulting from the desired ring closure at C-1′ was obtained in all the runs, but in disappointingly low yields. The best yield of **16**,[8] i.e., 21%, was obtained in an experiment using the sodium base in refluxing THF. The substitution of DME for THF did not lead to an improvement in the yield. Approximately 30% of the

starting material was recovered in most of the experiments, but the bulk of the reaction mixture was composed of a highly polar material which could not be characterized.



Examination of models suggested that a furanone derivative such as **9** with a bulky hydroxyl-protecting group at C-3′ and a *cis* 4′,5′-double bond might have an appropriate geometry as well as a favorable conformation for ring closure. Coupling of the vinyl bromide **10** with the THP derivative of propargyl alcohol **11b** gave compound **12b**[8] in 70% yield. Hydroxylation of the terminal methylene group of the enyne with OsO_4-N-methylmorpholine-N-oxide (NMO) followed by cleavage of the crude diol with sodium metaperiodate[11] gave the enone **13**[8] in 44% overall yield. Treatment of **13** with $NaBH_4$-$CeCl_3$[12] led to selective reduction of the carbonyl group in the side chain to give a racemic diastereomeric mixture of C-3′ alcohols which was converted into a racemic mixture of t-butyldiphenylsilyl derivatives with TBDPSCl in the presence of imidazole. ^1H NMR and TLC analysis of this mixture indicated that the ratio of racemic diastereomers was approximately 4:1. Subsequent transformations revealed that the major racemic diastereomer in this mixture had the relative configuration shown in structure **14**.[8] Catalytic hydrogenation of the triple bond in **14** with $Pd/BaSO_4$ poisoned with quinoline in ethanol[13] gave a mixture of *cis* alkenes (51% yield) with the racemic diastereomer **15**[8] being the major component. Treatment of this mixture with CBr_4/PPh_3 led to the direct conversion of the THP-protected alcohols to the corresponding mixture of bromides[14] with the racemic diastereomer **9**[8] being the major product. Again, ^1H NMR spectroscopy and TLC analysis indicated that **9** and its racemic diastereomer were present in a *ca.* 4:1 ratio.

Cycloalkylation reactions of the diastereomeric mixture of bromo furanones containing mainly racemic **9** were conducted as previously described for bromo furanone **8**. In this case, the best results were otained when lithium hexamethyldisilazane was employed as the base in THF at -78°C and cycloalkylation product **17a** was obtained in greater than 53% crude yield. Because chromatographic separation of this compound from a minor, unidentified by-product was difficult, the TBDPS protecting group was removed with tetra-n-butylammonium fluoride (TBAF) in THF to give the alcohol **17b**,[8] which was isolated as the essentially pure material by preparative thin layer chromatography. The stereochemistry and conformation of **17b** was established by COSY and NOE ^1H NMR experiments.[15] The presence of a relatively large coupling constant (J=9.5Hz)

between the C-3 proton on the carbon bearing the oxygen atom and the adjacent C-4 vinyl proton and the fact that irradiation of the C-5 vinyl proton caused an NOE enhancement of the signal for one of the C-7 protons which in turn produced an NOE enhancement of the vinyl proton signal at C-9 supported the stereochemical assignment. These results also indicated that the molecule exists primarily in a folded conformation with the furanone ring and the *cis* 4,5-double bond facing each other. The stereochemical assignment of **17b** indicated that the major racemic diastereomer of its monocyclic precursor has the relative configuration shown in structure **9**. Likewise, the major isomers of the intermediates leading to **9** would have the configuration shown in structures **14** and **15**.

Possible pathways for elaboration of compound **17b** into members of the heliangolide family of sesquiterpenes are being explored.

References and Notes

1. Partial support of this research by a grant (5R01CA41688) from the National Institutes of Health is gratefully acknowledged.
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15. We are grateful to Dr. Ken Belmore for carrying out the NMR experiments.

(*Received in USA* 1 *July* 1994; *accepted* 22 *July* 1994)