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SYNTHESIS OF SYN-7-BENZYLOXY-4-METHYLBICYCLO[2.2.1]HEPT-5-EN-2-ONE, AN INTERMEDIATE FOR THE SYNTHESIS OF STEROIDS AND TRICOTHECANES; TANDEM ANIONIC [1,3]-[3,3] SIGMATROPIC REARRANGEMENT

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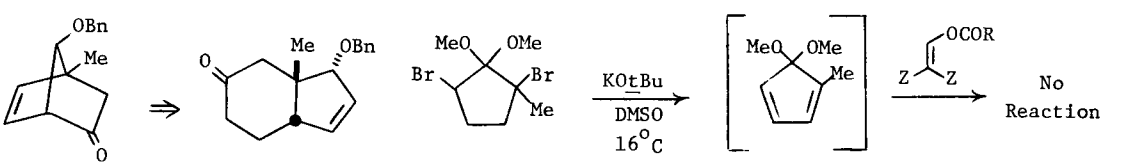
Abstract: The enone ether 1 has been prepared from 2-methylcyclopentenone and converted into the hydrindenone 2; the first example of a tandem anionic [1,3]-[3,3] sigmatropic rearrangement is reported.

Recently, several 7-oxygen-substituted norbornenones and norbornanones have found use in the preparation of intermediates for the total synthesis of various natural products and their analogues. For example, we reported the use of 7,7-dimethoxynorbornenone in the construction of steroid analogues via an anionic oxy-Cope rearrangement process,[3] while Roush described the preparation of a 5,7-dihydroxy-4-methylnorbornan-2-one as a potential precursor to verrucarol.[4] We now report the facile synthesis of syn-7-benzyloxy-4-methylbicyclo[2.2.1]hept-5-en-2-one 1 and describe its conversion into the angularly methyl-substituted hydrindenone 2 as a model for the synthesis of steroids. In addition, we report the first example of a tandem anionic [1,3]-[3,3] sigmatropic rearrangement process.

An adaptation of the work of Eaton[5] for the synthesis of intermediates to 1 proved unsuccessful. Treatment of the dibromide 3[6] with potassium t-butoxide in DMSO at 16°C presumably formed the diene 4. However, this diene did not undergo cycloaddition with the reactive dienophiles 5a or 5b,[7] although the dienophiles did react with cyclopentadiene in good yield.



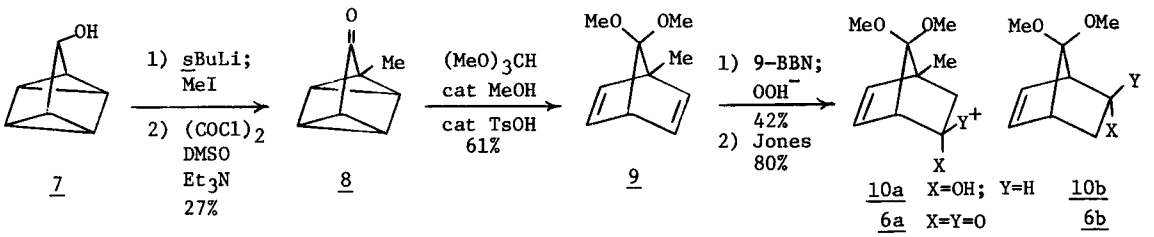
1 2 3 4

5a Z=CO_2Et; R=Me

5b Z=CN; R=p$NO_2C_6H_4$

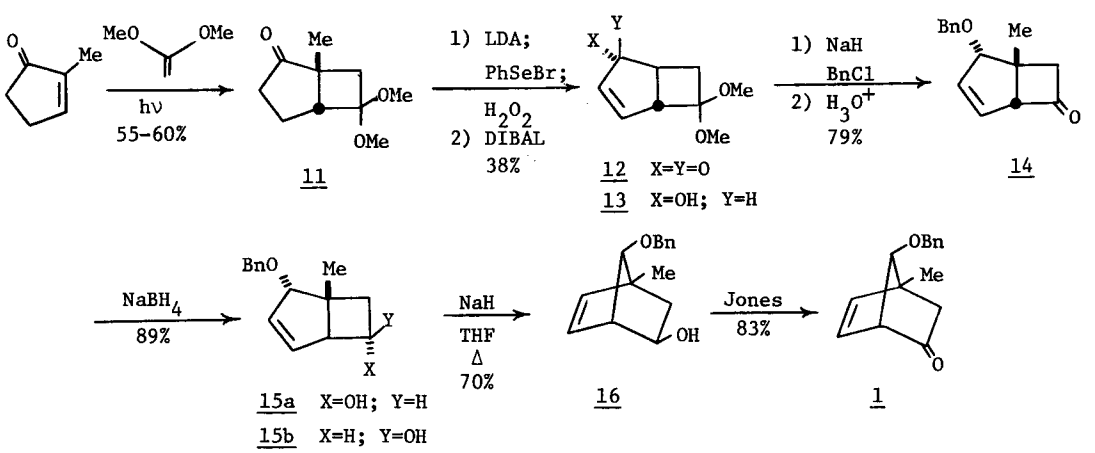
A second approach provided a regiochemical mixture of 6a and its 1-methyl isomer 6b, as potential intermediates for the synthesis of 1. Quadricyclanol 7[8] was deprotonated with 3.5-4 equiv of s-butyllithium and alkylated with 2.5-3 equiv of methyl iodide[10] to give a mixture of C-methylated quadricyclanols which were oxidized directly under Swern's conditions[11] and separated by chromatography to give the quadricyclanone 8 in 27% yield along with the 1,4-dimethylated (5%) and unmethylated (6%) compounds. Ketalization and concomitant opening of the quadricyclane system

occurred upon treatment of 8 with catalytic methanol in trimethyl orthoformate and p-toluenesulfonic acid to give the ketal 9 in 61% yield. Unfortunately, hydroboration of 9 with 9-borabicyclo[3.3.1]nonane (9-BBN) gave, after oxidation with basic hydrogen peroxide, a 42% yield (with 37% recovered 9) of a 1:1 mixture of the regioisomeric endo alcohols 10ab which could be oxidized to a 1:1 mixture of 6ab. The difference in the steric environments of the two carbons of the olefins is evidently not great enough to allow any regioselectivity in the hydroboration process.



7 8 9 10a X=OH; Y=H 10b 6a X=Y=O 6b

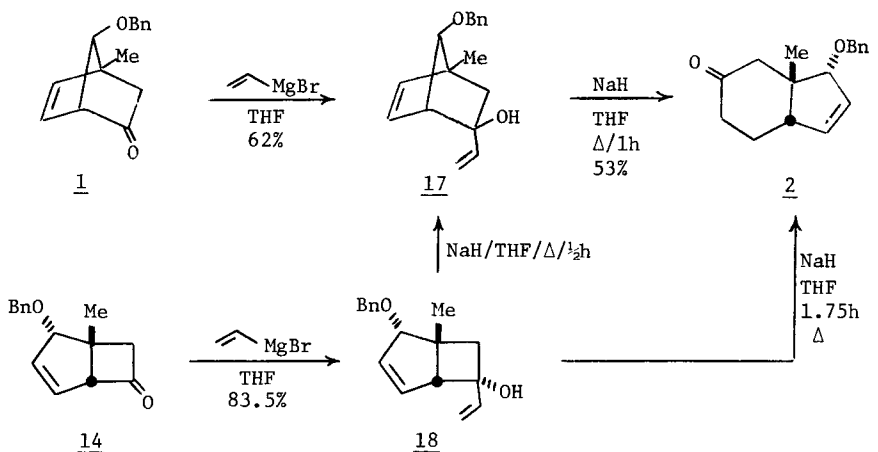
The final successful approach to 1 was based on the anionic modification[11] of the [1,3] sigmatropic rearrangement of bicyclo[3.2.0]heptenols originally described in detail by Berson.[12] Photolysis of 2-methylcyclopentenone and ketene dimethyl acetal in benzene gave (55-60%) a 6:1 mixture of 11 and its regiochemical isomer which were easily separated by preparative HPLC. Introduction of unsaturation by the normal method (LDA, PhSeBr, H_2O_2) gave, in addition to recovered 11 (27%), the enone 12 (53%) which was reduced to mainly the endo alcohol 13 by treatment with DIBAL (72%). Benzylation and hydrolysis produced in 73% yield the enone ether 14, which was reduced by sodium borohydride to a mixture of alcohols 15ab (89% yield), in which the endo alcohol 15a predominated. These alcohols did not have to be separated since both were rearranged to the same norbornenol in the next step. Treatment of 15ab with sodium hydride[13] in refluxing THF for 30 min gave a 70% yield of only the exo alcohol 16. The fact that the endo alcohol rearranges with retention and the exo with inversion to both give 16 is consistent with the results of Berson[12] and Wilson[11]. Jones oxidation of 16 cleanly afforded 1 in 83% yield, thus making it available in reasonable quantity from 2-methylcyclopentenone in 8% overall yield.



11 12 X=Y=O 13 X=OH; Y=H 14 15a X=OH; Y=H 15b X=H; Y=OH 16 1

With 1 in hand, we turned our attention to its use in synthesis and chose to first investigate its application in steroid chemistry. Addition of vinylmagnesium bromide occurs exclusively from the desired endo direction, due to the steric hindrance of the benzyloxy group on the exo face of the ketone, to give the dienol 17 in 62% yield. Treatment of 17 with sodium hydride in refluxing THF for 1h afforded the desired methyl-substituted hydrindenone 2 in 53% yield along with 12% recovered 17. Thus, one of the major drawbacks of this anionic oxy-Cope approach to steroids,[3] namely the introduction of the 18-methyl group, has now been overcome with the preparation of 1 and its conversion to 2.[14]

The stereochemistry of the reduction of 14 and the ease of the anionic [1,3] sigmatropic rearrangement suggested an alternative route to 2, namely the possibility of a tandem anionic [1,3]-[3,3] sigmatropic rearrangement. Thus, addition of vinylmagnesium bromide to 14 occurs predominately from the exo face as expected to give the endo alcohol 18 (83.5%). This compound is now set up to undergo an anionic [1,3] sigmatropic shift with retention to produce the sodium salt of the exo alcohol 17 which should then undergo the anionic [3,3] sigmatropic shift to give 2. In fact, this scenario is followed but only in fair to poor yield. Rearrangement of 18 under mild conditions (NaH, refluxing THF, 30 min) followed by aqueous workup produced the alcohol 17 as the major product with only a trace of 2 being formed.[15] However, when 18 was rearranged under more vigorous conditions (NaH, refluxing THF, 1.75 h), none of the alcohol 17 could be detected but the hydrindenone 2 was isolated in 10% yield. Thus, although a direct [1,3] sigmatropic rearrangement of 18 to 2 cannot be ruled out,[16] these results are best explained by a tandem [1,3]-[3,3] sigmatropic process.[17]



Further reactions of 2 and the use of 1 as a synthon for other natural products, i.e., the trichothecanes, are currently under investigation.

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References and Notes

(1) Camille and Henry Dreyfus Teacher-Scholar, 1978-83; Fellow of the Alfred P. Sloan Foundation, 1979-81.

(2) Fellow of the Chevron Oil Co., Inc., at UCLA.

(3) Jung, M. E.; Hudspeth, J. P. J. Am. Chem. Soc. 1978, 100, 4309.

(4) Roush, W. R.; D'Ambra, T. E. J. Org. Chem. 1981, 46, 5045.

(5) Eaton, P. E.; Hudson, R. A. J. Am. Chem. Soc. 1965, 87, 2769.

(6) Prepared from 2-methylcyclopentanone by ketalization (trimethyl orthoformaate, methanol, pTsOH, 77%) and bromination (pyridium bromide perbromide, methanol, 57% crude). All new compounds exhibited spectral data (^{1}H and ^{13}C NMR, IR, MS) in complete accord with the assigned structures.

(7) Prepared by hydroxymethylenation of diethyl malonate or malononitrile followed by acylation with acetic anhydride in pyridine or p-nitrobenzoyl chloride in ether. These compounds were designed as ketene equivalents with regiochemical control opposite tothe known ketene equivalents in Diels-Alder reactions. Cycloaddition, hydrolysis, oxidation and decarboxylation would produce the desired ketone.

(8) Prepared by the following modification of the known route:[9] 7-benzoyloxynorbornadiene was irradiated in cyclohexane to give 81% of quadricyclanol benzoate which wassaponified (1N sodium hydroxide in tetrahydrofuran) to give 7 in 79% yield.

(9) (a) Tanida, H.; Tsuji, T. J. Org. Chem. 1964, 29, 849; (b) Buldt, E.; Friedrichsen, W. Justus Liebigs Ann. Chem. 1977, 1410.

(10) This is a slight variation of the method of Klumpp who used isopropyllithium. Klumpp, G. W.; Kool, M.; Schakel, M.; Schmitz, R. F.; Boutkan, C. J. Am. Chem. Soc. 1979, 101, 7065.

(11) Wilson, S. R.; Mao, D. T. J. Chem. Soc. Chem. Commun. 1978, 479.

(12) Berson, J. A. Acc. Chem. Res. 1968, 1, 152.

(13) The use of potassium hydride in these systems leads to complications due to loss of the allylic benzyloxy group. Similar results in other systems[3] have led us in such cases to use sodium hydride, which minimizes these problems.

(14) In order to apply this route to a synthesis of steroids, the CD-ring juncture stereochemistry must be trans. There are methods to deconjugate the D-ring enone (Afonso, A. J. Am. Chem. Soc. 1968, 90, 7375) and reduce catalytically to give mainly the trans stereochemistry (Rufer, C.; et al. Justus Liebigs Ann. Chem. 1967, 705, 211) in the literature.

(15) Gadwood has reported one further example of an anionic [1,3] sigmatropic shift of a divinyllic cyclobutanol. In that case, although a further anionic [3,3] sigmatropic rearrangement was possible, it did not occur. Presumably alcohol 18 undergoes some of the other rearrangements described by Gadwood (isomerization to the cis-1,2-divinyllic cyclobutane, [3,3] rearrangement of the cis isomer, anionic retroene reaction) upon treatment with sodium hydride, thereby lowering the yield of 17 and 2. Gadwood, R. C.; Lett, R. M. J. Org. Chem. 1982, 47, 2268.

(16) Other anionic [1,3] sigmatropic shifts have been described: Thies, R. W.; Seitz, E. P. J. Org. Chem. 1978, 43, 1050. Danheiser, R. L.; Martinez-Davila, C.; Sard, H. Tetrahedron 1981, 37, 3943.

(17) Tice, C. M.; Heathcock, C. H. J. Org. Chem. 1981, 46, 9, reported a similar overall requirement although the intermediate [1,3]-rearrangement product was not isolated.

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