SYNTHESIS OF SYN-7-BENZYLXY-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-methynorbornan-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 Eaton5 for the synthesis of intermediates to 1 proved unsuccessful. Treatment of the dibromide 36 with potassium tert-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, although the dienophiles did react with cyclopentadiene in good yield.

A second approach provided a regiochemical mixture of 6a and its 1-methyl isomer 6b, as potential intermediates for the synthesis of 1. Quadricyclanol 18 was deprotonated with 3.5-4 equiv of s-butyllithium and alkylated with 2.5-3 equiv of methyl iodide10 to give a mixture of C-methylated quadricyclanols which were oxidized directly under Swern's conditions11 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-toluene-
sulfonic acid to give the ketal 9 in 61% yield. Unfortunately, hydroboration of 9 with 9-bora-
bicyclo[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 ole-
fins is evidently not great enough to allow any regioselectivity in the hydroboration process.

The final successful approach to 1 was based on the anionic modification\(^\text{11}\) of the [1,3] sig-
matropic rearrangement of bicyclo[3.2.0]heptenols originally described in detail by Berson.\(^\text{12}\) Pho-
tolysis of 2-methylcyclopentenone and ketene dimethyl acetal in benzene gave (55-60%) a 6:1 mi-
ture of 11 and its regiochemical isomer which were easily separated by preparative HPLC. Intro-
duction 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\(^\text{13}\) 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\(^\text{12}\)
and Wilson\(^\text{11}\). Jones oxidation of 16 cleanly afforded 1 in 83% yield, thus making it available in
reasonable quantity from 2-methylcyclopentenone in 8% overall yield.
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 hydrindene 2 in 53% yield along with 12% recovered 17. Thus, one of the major drawbacks of this anionic oxy-Cope approach to steroids, 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 hydrindene 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


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


(6) Prepared from 2-methylcyclopentanone by ketalization (trimethyl orthoformate, methanol, pTsOH, 77%) and bromination (pyridinium bromide perbromide, methanol, 57% crude). All new compounds exhibited spectral data (H and 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 to the 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: 7-benzoyloxybornadiene was irradiated in cyclohexane to give 81% of quadricyclanol benzoate which was saponified (1N sodium hydroxide in tetrahydrofuran) to give 7 in 79% yield.


(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.


(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 have led us to 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.


(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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