

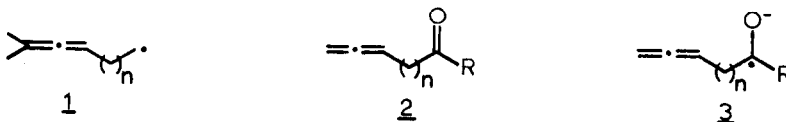
REDUCTIVE CYCLIZATIONS OF ALLENIC KETONES BY DISSOLVING METALS

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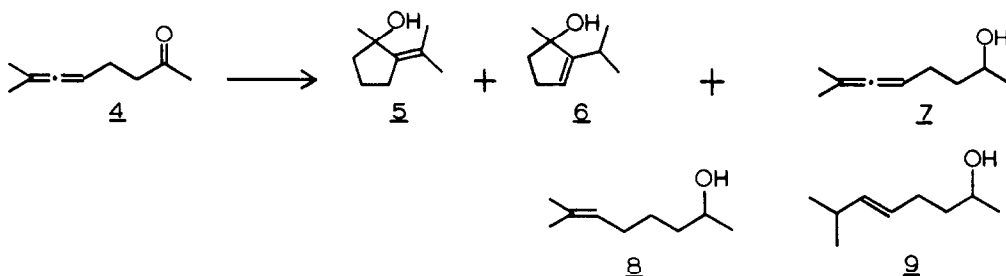
Summary: The dissolving metal reductions of certain allenic carbonyl compounds leads to the formation of cyclic alcohols with high regioselectivity.

We have recently reported on the cyclizations of ω -allenyl radicals 1.¹⁻³ This process constitutes a useful method for the formation of carbocyclic compounds in some instances. In related work, we have examined the reductions of allenic carbonyl compounds of general structure 2 with dissolving metal reagents likely to generate radical-anion 3. The enhanced stability of such radical anions relative to radicals of type 1 was considered as potentially advantageous for cyclization. A subsequent report by Pattenden demonstrates the use of electrochemical methods for reductive cyclization of several allenic ketones.⁴ Our initial results on cyclizations of 2 by chemical methods are the subject of this communication.



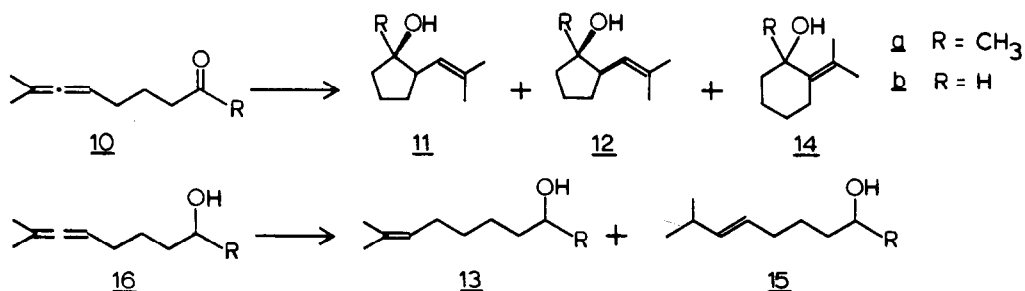
Reaction of 7-methylocta-5,6-dien-2-one⁵ (4) with 4 equiv of sodium naphthalenide in THF at room temperature for 5 hours, followed by removal of naphthalene by column chromatography over silica gel, gave a 46% yield of three products as a 67:30:3 mixture. The two major components were shown to be isomeric alcohols 5 and 6, respectively.⁶ The minor component was not identified, but it was demonstrated that neither allenic alcohol 7,⁵ nor its further reduction products were present. Similar results were obtained by

ultrasound activation of a mixture of 4 with 4 equiv of metallic sodium in THF for 4 hours. In this case a 63:27:6:4 mixture of 5, 6, 7 and an unidentified compound was obtained from which a 44% yield of the two cyclic alcohols could be isolated by chromatography. A large excess of lithium in liquid ammonia--THF containing tert-butanol gave a 23:39:21:9:5:3 mixture of 5, 6, 8, 9 and two unknown compounds in 66% yield. The olefinic alcohols 8 and 9 were also obtained as the major products from reduction of alcohol 7 under these conditions. Attempts to examine the reductive behavior of 6-methylhepta-4,5-dienal were thwarted by the propensity of this aldehyde to decompose spontaneously.⁹



The homologous ketone 8-methylnona-6,7-dien-2-one¹⁰ (10a) reacted with 3 equiv of sodium naphthenide in THF to give a 75:10:6:1:5:3 mixture of six products in 53% yield. The first two components were shown to be the isomeric cyclopentanol 11a and 12a by comparison with authentic materials.¹¹ The third component had spectral properties in accord with alcohol 13a and the fourth had a glc retention time identical with that of cyclohexanol 14a¹². The other two products were not identified. Reduction of 10 with lithium and tert-butanol in liquid ammonia--THF gave a 66:34 mixture of alcohols 13a and 15a in 58% yield without significant amounts of cyclic products.

The reduction of 7-methylocta-5,6-dienal¹⁴ (10b) with 3 equiv of sodium naphthalenide gave a 27:7:48:14:4 mixture of alcohols in 59% yield. The first four of these products were identified as 11b, 12b,¹⁵ 13b and 15b, respectively; the remaining component was not identified. A 76:24 mixture of 13b and 15b was also obtained by the reduction of allenic alcohol 16b¹⁶ by lithium in liquid ammonia.



These results provide further support to the idea that radical anions of type 3 can cyclize in a manner similar to that of the simple radicals 1. The product yields in these conversions are modest and the desired cyclic alcohols are accompanied by varying amounts of acyclic alcohols. Nonetheless, the overall transformations have considerable synthetic potential. Ketone 4 undergoes a particularly easy cyclization, which is competitive even in a lithium--ammonia reduction. This facility of cyclization is similar to that of the analogous simple radical, as is the highly regioselective addition of the radical center to the central allenic carbon, which results in efficient five-ring formation.¹ A mixture of cyclic alcohols is formed in this case, presumably by further reduction of the cyclic radical, followed by protonation at either end of the allylic anion thus generated. Ketone 10a appears to be less effective at cyclization, since only acyclic products were characterized from a lithium--ammonia reaction. Once again highly regioselective formation of a cyclopentane ring is observed upon sodium naphthalenide reduction. In this instance radical-anion attack at the more proximate allenic carbon obtains. This cyclization is more selective than that of the analogous simple radical 1, which gives significant amounts of both five- and six-ring products.¹ There is also some stereoselectivity (75:10) in favor of the cyclopentanol with hydroxy and vinyl groups trans to each other. The corresponding aldehyde 10b behaves similarly, except that cyclization is less competitive with reduction to acyclic alcohols. We are currently attempting to expand the scope of these cyclizations and to adapt them to synthetic objectives.

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6. Alcohol **5** was prepared by methyllithium addition to 2-isopropylidenecyclopentanone:⁷ mp 60-61°C; IR 3320, 1360, 1180 cm⁻¹; NMR δ 1.35 (s, 3), 1.60 (s, 3), 1.88 (s, 3), 1.5-2.0 (m, 4), 2.2 (m, 2). Alcohol **6** was synthesized by methyllithium addition to 2-isopropylcyclopent-2-en-1-one:⁸ IR 3360, 3015, 1660, 1360, 1380, 1180, cm⁻¹; NMR δ 1.08 (d, 3, J = 6 Hz), 1.16 (d, 3, J = 6 Hz), 1.32 (s, 3), 1.5-2.5 (m, 6), 5.45 (br s, 1).
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9. 6-Methylhepta-4,5-dienal was prepared by Swern oxidation (ClCOCOCl, DMSO, Et₃N) of the corresponding alcohol:¹ IR 2700, 1970, 1720, 1370 cm⁻¹; NMR δ 1.65 (d, 6, J = 3 Hz), 2.2-2.7 (m, 4), 5.05 (m, 1), 9.80 (m, 1).
10. Ketone **10a** was prepared by alkylation of 1-lithio-3-methyl-1,2-butadiene¹ with the ethylene ketal of 5-bromo-2-pentanone and hydrolysis: IR 1970, 1710, 1360 cm⁻¹; NMR δ 1.65 (d, 6, J = 3 Hz), 2.06 (s, 3), 1.6-2.1 (m, 4), 2.32 (t, 2), 4.85 (m, 1).
11. Alcohol **11a** showed: IR 3380, 1380, 1140 cm⁻¹; NMR δ 1.15 (s, 3), 1.65 (s, 3), 1.71 (s, 3), 1.5-2.7 (m, 8), 4.90 (br d, 1, J = 10 Hz). Alcohol **12a** showed: IR 3460, 1370, 1150 cm⁻¹; NMR δ 1.14 (s, 3), 1.60 (s, 3), 1.71 (s, 3), 1.4-2.5 (m, 8), 5.08 (br d, 1, J = 10 Hz). A mixture of **11a** and **12a** was obtained by methyllithium addition to 2-(2'-methyl-1'-propenyl)-cyclopentanone.
12. Alcohol **14a** was prepared by methyllithium addition to 2-isopropylidenecyclohexanone.¹³ It showed: mp 62-65°C; IR 3380, 1440, 1100 cm⁻¹; NMR δ 1.35 (s, 3), 1.69 (s, 3), 1.98 (s, 3), 1.3-2.7 (m, 9).
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14. Swern oxidation of **16b** gave **10b**: IR 2700, 1970, 1720 cm⁻¹; NMR δ 1.65 (d, 6, J = 3 Hz), 1.2-2.1 (m, 4), 2.35 (t, 2), 4.85 (m, 1), 9.95 (m, 1).
15. Alcohol **11b** was prepared by addition of 2-methyl-1-propenylmagnesium bromide--CuI to 1,2-epoxycyclopentane: IR 3400, 1370, 1040 cm⁻¹; NMR δ 1.65 (br s, 3), 1.72 (br s, 3), 1.1-2.1 (m, 7), 2.45 (m, 1), 3.69 (m, 1), 4.90 (br d, 1, J = 9 Hz). Oxidation of **11b** with pyridinium dichromate followed by reduction with LiBEt₃H gave a 1:1 mixture of **11b** and **12b**: IR 3340, 1375, 1050 cm⁻¹; NMR δ 1.63 (br s, 3), 1.75 (br s, 3), 1.3-2.1 (m, 7), 3.9 (m, 1), 5.12 (br d, 1, J = 9 Hz).
16. Addition of methylmagnesium bromide--CuI to 2-(1'-propynyl)tetrahydropyran¹⁷ gave **16b**: IR 3320, 1970, 1050 cm⁻¹; NMR δ 1.65 (d, 6, J = 3 Hz), 1.3-2.0 (m, 6), 2.75 (m, 1), 3.42 (t, 2), 4.85 (m, 1).
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