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ORGANOCUPRATE REACTIONS OF ENONE LACTONES.

I. SYNTHESIS OF TRANS-FUSED RINGS VIA CONJUGATE ADDITION.

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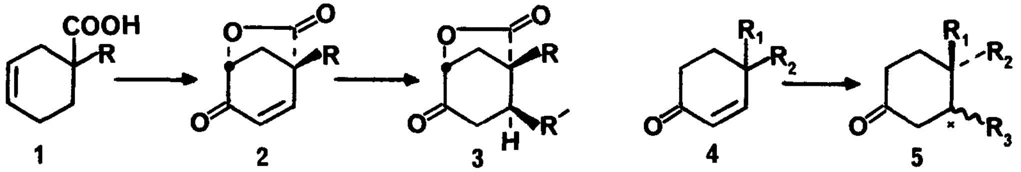
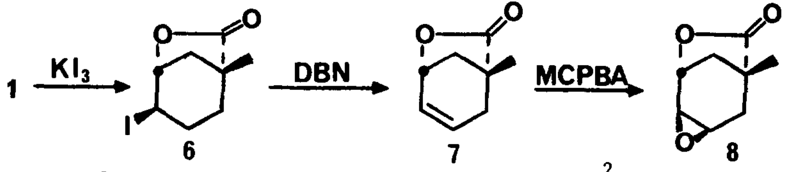
Abstract: Control of the stereochemistry of substituents needed to construct a bicyclic system (e.g. a hydrindanone) is achieved by conjugate addition of an organocuprate to a cyclohexenone made conformationally rigid by the attachment of a 1,3-lactone.

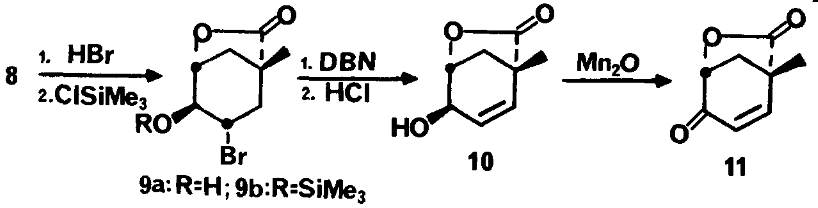
We wish to describe a new construction of *trans*-fused ring systems which is based on the conjugate addition of organocuprates to lactonic enones of type 2.



The conjugate addition of an organocuprate to a 4,4-disubstituted cyclohexenone such as 4 cannot presently achieve stereocontrol at the starred position in 5. This is unfortunate since enones 4 are readily available, and stereodefined 3,4,4-trisubstituted cyclohexanones such as 5 would be ideal precursors, *inter alia*, of *cis* or *trans* bicyclic systems. We illustrate here a solution to this problem of steric control which we achieve by imposing a rigid conformation on the cyclohexenone system 4, thus defining unequivocally the direction of addition of the eventual R_3 group. We demonstrate the validity of this approach by the construction of *trans*-8-methyl-1,5-hydrindandione, 20.[1]

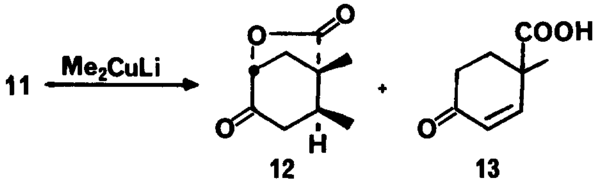


Treatment of 1-methyl-3-cyclohexenoic acid (1, R=CH_3)[2] with iodine and potassium iodide in aqueous sodium bicarbonate afforded iodolactone 6 in 97% yield (mp 103.5-104°, benzene-pentane). Lactone 6 was refluxed for 7hr with 1.2eq of diazabicyclononene in benzene, to give 7 (94% yield; mp 51-51.5°, sublimed at 0.15mm and 55°). Treatment of 7 for 11hr with

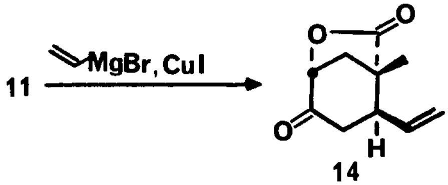


1.2eq of *m*-chloroperbenzoic acid in refluxing chloroform gave epoxylactone 8 (87% yield; mp 62-63°, ether-pentane).

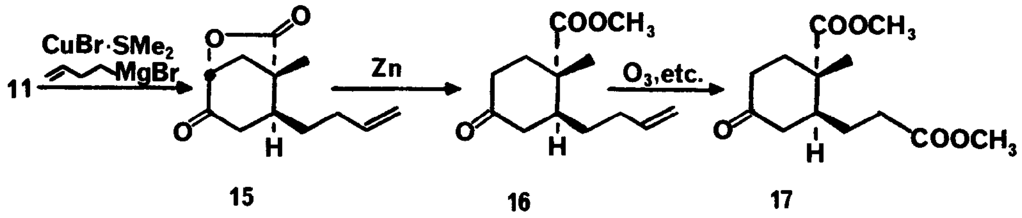
Exposure of epoxylactone 8 to 1.5eq of 48% HBr in chloroform at 0° resulted in precipitation of bromohydrin 9a (91% yield; mp 158-160°, ether-ethyl acetate). Quantitative conversion of 9a to silyl ether 9b (mp 83-85°, ether-pentane) was achieved by exposure to excess chlorotrimethylsilane in pyridine-tetrahydrofuran at 0°. Treatment of 9b with 1.2eq of diazabicyclononene in refluxing dioxane for 12hr, followed by hydrolysis with 1N HCl in acetone, afforded the allylic alcohol 10 (86% yield; mp 96-97.5°, ether-pentane). Lactone 10 was converted to enone lactone 11 (mp 44-46°, ether-pentane) in 84% yield by oxidation with freshly prepared manganese dioxide[3] in methylene chloride. Lactone 11 was thus obtained in >50% overall yield from the cyclohexenoic acid 1.



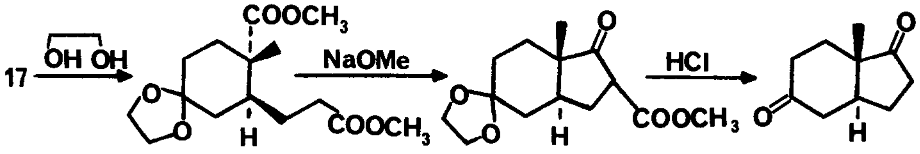
Exposure of enone 11 to 2eq of lithium dimethylcuprate in tetrahydrofuran at 0°, followed by workup with aqueous ammonium chloride, gave ketolactone 12 (51% yield; mp 75-77°, ether-pentane)[4], while acidification and ether extraction additionally furnished the ketoacid 13 in 39% yield. The latter product arises from the competitive reduction of 11 by lithium dimethylcuprate, a process well precedented for ketones substituted at the α-position with reducible groups.[5,6]



Vinylation may be performed by addition of enone 11 to a mixture of 2eq of vinylmagnesium bromide and 2eq of cuprous iodide in tetrahydrofuran at -78°, followed by gradual warming to 0°.[7] Workup with aqueous ammonium chloride and chromatography on silica gel afforded the ketolactone 14 in 47% yield. Further possibilities are demonstrated in the following sequence.



Addition of enone 11 to a mixture of 2eq of cuprous bromide-dimethylsulfide[8] and 2eq of 1-bromomagnesium-3-butene in tetrahydrofuran-dimethylsulfide (4:1) at -10°, followed by workup with aqueous ammonium chloride and chromatography on silica gel, gave the ketolactone 15 (mp 62-63°, ether-pentane) in 74% yield. No attempt was made to optimize the conditions of this and the other conjugate additions to 11. Exposure of 15 to a tenfold excess of zinc dust in refluxing acetic acid, followed by esterification with ethereal diazomethane, gave ketoester 16. Ozonolysis of 16 in methylene chloride at -78°, followed by treatment with zinc dust in acetic acid, excess Jones reagent in acetone, and ethereal diazomethane, provided, after chromatography on silica gel, the ketodiester 17 in 71% yield from 15. Ketalization of 17 with ethylene glycol in refluxing benzene containing *p*-toluenesulfonic acid afforded the crystalline diester 18 (mp 103-105°, ether-pentane), which was identical in all respects with an authentic sample.[9]



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The diester 18 was cyclized by refluxing for 16hr with 10eq of sodium methoxide in benzene, to produce the hydrindanone 19 (61% yield; mp 97-97.5°, ether-pentane).[10] Hydrolysis of 19 with 6N HCl in refluxing acetic acid for 1.5hr, followed by chromatography on silica gel, furnished in 75% yield the known *trans*-8-methyl-1,5-hydrindandione 20, mp 51-53°.

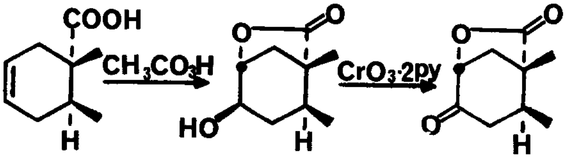
There exist in the literature a number of construction methods which may be better suited to a specific *cis* or *trans* bicyclic system (including *trans* hydrindanediones) but the flexibility and generality of the sequence outlined here should prove valuable.[11]

Acknowledgment: We thank the National Science Foundation and the National Institutes of Health for support of this work.

References and Notes

1. New compounds had spectral data consistent with assigned structures, and crystalline compounds gave satisfactory elemental analyses. Capillary melting points were determined on a Büchi "schmelzpunktbestimmungsapparat" and are uncorrected.
2. A.A. Petrov and N.P. Sopov, *Zh. Obshchei Khim.*, 18, 1781 (1948).
3. J. Attenburrow, A.F.B. Cameron, J.H. Chapman, R.M. Evans, B.A. Hems, A.B.A. Jansen, and T. Walker, *J. Chem. Soc.*, 1952, 1094.

4. The stereochemistry assigned to 12 was verified by independent synthesis from the Diels-Alder adduct of butadiene with tiglic acid, 22 (H.O. House and W.F. Gilmore, J. Am. Chem. Soc., 83, 3980 (1961)):



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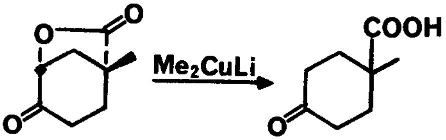
5. J.R. Bull and A. Tuinman, Tetrahedron Lett., 1973, 4349.

6. We have observed that simple saturated keolactones may undergo reductive cleavage under these conditions:



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11. For another general predictable sequence, see reference 9.

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