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# CONJUGATIVE γ-LACTONE ANNULATION: ONE-POT HYDROBORATION-OXIDATION OF HOMOALLYLIC ALCOHOL TRIMETHYLSILYL ETHERS

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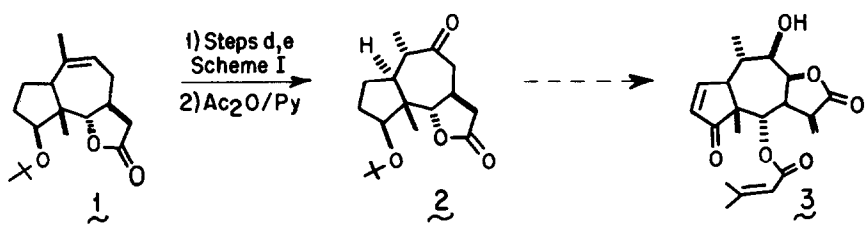
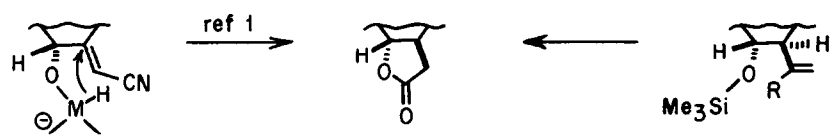
Abstract: Products from stereospecific vinylcuprate addition to hydroazulenic γ-trimethylsiloxy-α,β-unsaturated cycloheptenones are converted directly to trans-fused γ-lactones by 1) $BH_3$-THF, 2) B-H hydrolysis, and 3) PCC oxidation.

In the preceding Letter, a stereospecific lactone annulation sequence featuring intramolecular, conjugate reduction of α,β-unsaturated nitriles was reported.[1] It was deemed essential to know the configuration of the new trans-lactone stereocenters relative to other chiral centers in 1 and derivative 2, which is destined for ultimate transformation into fastigilin C (3) and other pseudoguaianolides.[2]




1 2 3

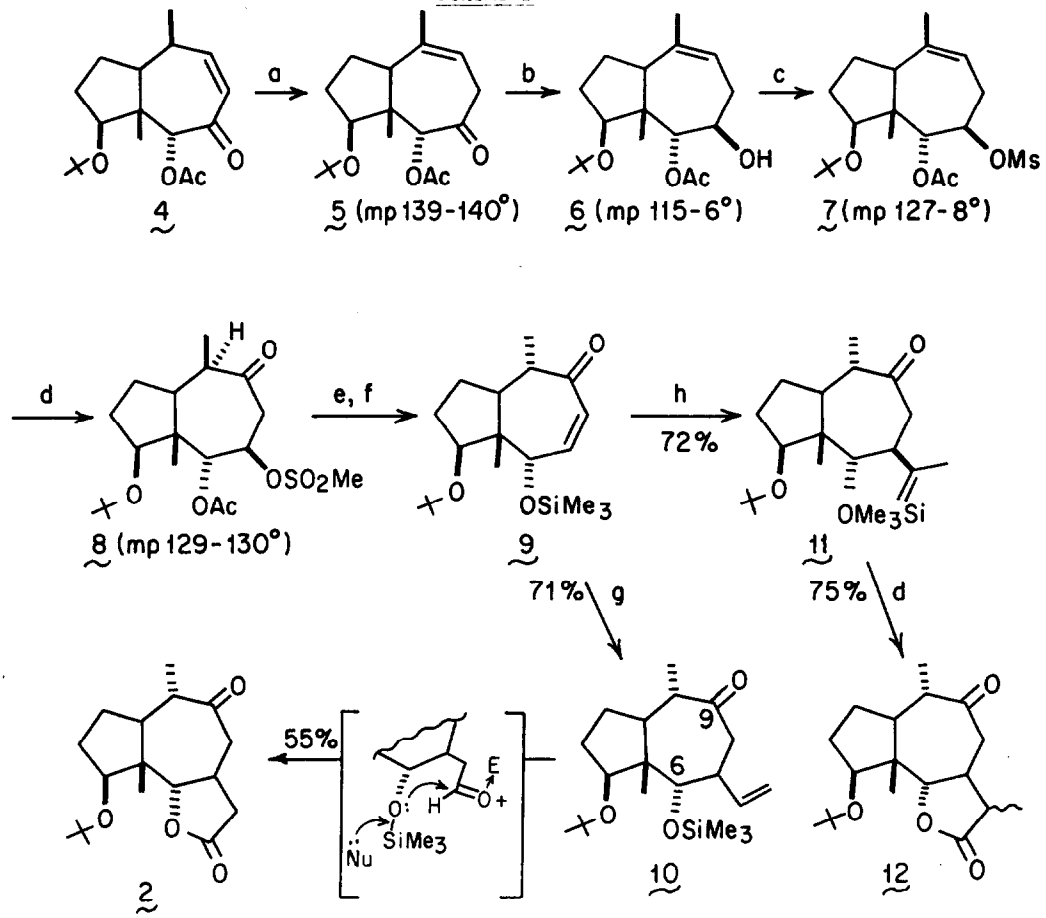
An alternative and complementary route to 2 is described below, in which lactone ring fusion stereochemistry is established during intermolecular conjugate addition of simple vinyl cuprates to γ-trimethylsiloxycycloheptenones from the side opposite the bulky $(CH_3)_3SiO$-substituent.




Consecutive introduction of borane, water and pyridinium chlorochromate (PCC) then generates the lactone in one experimental operation.

It is known that trialkylboranes can be oxidized directly by $Cr^6$ reagents to aldehydes and ketones.[3] However, the sterically-hindered environment of our alkene groups, especially in 1 and 5, necessitated the use of excess borane (→$RBH_2$) and thus hydrolysis of residual B-H bonds, without deblocking trimethylsilyl-protected alcohols, before PCC oxidation.[4] Scheme I illustrates the steps[5] by which keto-lactone 2, mp 154-155°, can be readily prepared from 4, in which the acetate group was known to be α-oriented.[1]

Scheme I




Reagents: a) DBU/$CH_2Cl_2$, Δ, 7 h; b) $NaBH_4$/$CH_3OH$-THF, -10°→20°, 1 h; c) $CH_3SO_2Cl/Et_3N$, 0→20°, 1 h; c) $CH_3SO_2Cl/Et_3N$, 0→20°, 1 h; d) 2 eq. $BH_3$-THF, 5 eqs. $H_2O$, 3 eqs. PCC/$CH_2Cl_2$, 20 h, RT (see procedure); e) LiOH/DME-$H_2O$, 20°, 24 h; f) $Me_3SiCl$, $Et_3N$, 4-DMAP/$CH_2Cl_2$, 20 h, RT; g) $LiCu(CH=CH_2)_2$, 0°, 2 h; h) $CH_2=C(MgBr)CH_3$, CuBr·DMS/$Et_2O$.

1,3-Transposition of the α,β-unsaturated carbonyl unit of 4 into 9, mp 80-82°, accompanied by C-10 methyl epimerization, proceeded in 50% overall yield (for six steps). 9 did not react with silyl ketene acetals[6] or the functionalized vinyl cuprate reagents of Marino[7a] and Boeckman.[7b] However, lithium divinylcuprate was readily introducable (9→10, 71%) at the sterically hindered β-position of this conjugated ketone. Copper-catalyzed 1,4-addition of 2-propenylmagnesium bromide to 9 also proceeded smoothly, affording 11, mp 93-4°, in 72% yield. Subsequent hydroboration-oxidation of 11 provided 12, as a mixture of C-11 epimers, in 75% yield, thus introducing a potential intermediate for pseudoguaianolides with α-methyl-γ-lactone structural units.[8]

We are as yet uncertain of the mechanistic details of the oxidative lactonizations of 10 and 11 which follow hydroboration of the double bonds. Certainly, some borane reduction of the ketone centers takes place concomitantly; reoxidation at C-9 occurs when PCC is used at the same time that the TMS ether retards premature C-6 oxidation. One may speculate that the aldehyde group, coordinated with some acidic species during PCC oxidation, electrophilically attacks the C-6 oxygen (Scheme I), thus promoting desilylation and further oxidation of the transient lactol intermediate. Similar oxidative cyclizations onto π-bonds with PCC have been observed by Corey and Boger.[9]

Two mechanistically different and stereorational syntheses of 2 have now been completed and each one introduces a valuable trans-lactone annulation[10] for broader use in natural products chemistry. Of special merit in this instance is our successful conjugate addition of simple vinyl cuprates to hindered cycloalkenones[11] such as 9, whereas unsatisfactory results are sometimes obtained with functionalized vinyl cuprates,[7] a not uncommon result in situations of extreme steric hindrance.[12] The "one-pot" hydroboration-oxidation of homoallylic alcohol TMS ethers such as 10 directly to a trans-fused γ-lactone more than compensates for the "missing" α-methylene grouping at this stage. The sensitivity of the latter moiety, which often requires multi-step blocking-deblocking sequences, dictates that α-methylenation be performed as late as possible in total synthesis. We are employing such a strategy in taking 2 on to complex pseudoguaianolides containing functional groups at C-6 and C-9 (e.g. 3) and will report on these studies in due course.

Preparation[13] of lactone 2:

Ketone 10 (126 mg, 0.33 mmol) in 1.0 mL of THF was treated with 1.0 mL of 1M $BH_3$ in THF for 1.5 h at 0°, then 0.5 h at 20°. Excess hydride was destroyed with 60 μL of $H_2O$ and solvent then evaporated. The residue was stirred in 10 mL $CH_2Cl_2$ with 750 mg (3.6 mmol) of PCC during 20 h at RT. The mixture was then filtered through florisil, with 1:1 ether-ethyl acetate and concentrated. The dark residue was saponified (NaOH in aq. DME, 20°, 3 h), then washed ($CH_2Cl_2$) and the alkaline aqueous layer acidified (pH 3). Extraction with $CH_2Cl_2$, drying ($MgSO_4$) and concentration was followed by $Ac_2O$ (0.1 mL) and pyridine (0.5 mL) in methylene chloride to ensure complete lactonization. Work-up afforded 53 mg (53%) of crystalline 2, mp 154-6°, ν 1780 $cm^{-1}$, MS m/e 308 ($M^+$) identical in all respects with material obtained from lactone 1 (ref. 1).

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## References and Notes

1. P. T. Lansbury and J. P. Vacca, Tetrahedron Lett., 23, 0000 (1982).

2. P. T. Lansbury, A. K. Serelis, J. E. Hengeveld and D. G. Hangauer, Jr., Tetrahedron, 36, 2701 (1980).

3. a) H. C. Brown, G. G. Rao and S. V. Kulkarni, J. Org. Chem., 44, 2809 (1979).
b) V. V. Ramana Rao, D. Devaprabhakara, and S. Chandrasekaran, J. Organomet. Chem., 162, C-9 (1978).

4. E. J. Corey and J. W. Suggs, Tetrahedron Lett., 2647 (1975).

5. All new compounds reported herein were fully characterized by an appropriate combination of PMR, IR, UV and MS analysis on chromatographically pure samples, along with C,H elemental analyses on all solids and most oils. Complete details may be found in the Ph.D. dissertation of T. E. Nickson, SUNY at Buffalo, February, 1982.

6. T. Mukaiyama, M. Osaki and K. Saigo, Chem. Lett., 163 (1976).

7. a) J. P. Marino and J. S. Farina, Tetrahedron Lett., 3901 (1975).
b) R. K. Boeckman, Jr. and M. Ramaiah, J. Org. Chem., 42, 1581 (1977).

8. eg. Radiatin: J. J. Einck, C. L. Herald, G. R. Pettit and R. B. VonDreele, J. Am. Chem. Soc., 100, 3544 (1978).

9. E. J. Corey and D. L. Boger, Tetrahedron Lett., 2461 (1978).

10. For trans→cis lactone inversion (at the carbinol center), see P. T. Lansbury, D. G. Hangauer, Jr. and J. P. Vacca, J. Am. Chem. Soc., 102, 3964 (1980).

11. Although 9 was prepared from 4 by a sequence involving enone transposition, other valuable hydroazulenic 6-oxyfunctionalized-7-ene-9-ones are accessible directly by intramolecular aldol condensations, from chiral intermediates. This makes the present method even more valuable (P. T. Lansbury and D. J. Mazur, unpublished observations).

12. For example, Heathcock et al (J. Org. Chem. 44, 4481 1979) obtained poor results in addition of lithium di-t-butylcuprate to 4-alkylcycloheptenones.

13. Ph.D. dissertation, T. E. Nickson, SUNY at Buffalo, 1982.

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