Tetrahedron Letters No. 44, pp 4205 - 4208.
©Pergamon Press Ltd. 1978. Printed in Great Britain.

0040-4039/78/1029-4205$02.00/0

# A NEW SYNTHETIC APPROACH TO PSEUDOGUAIANES.

A. Alexakis, M. J. Chapdelaine, G. H. Posner* and A. W. Runquist
Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

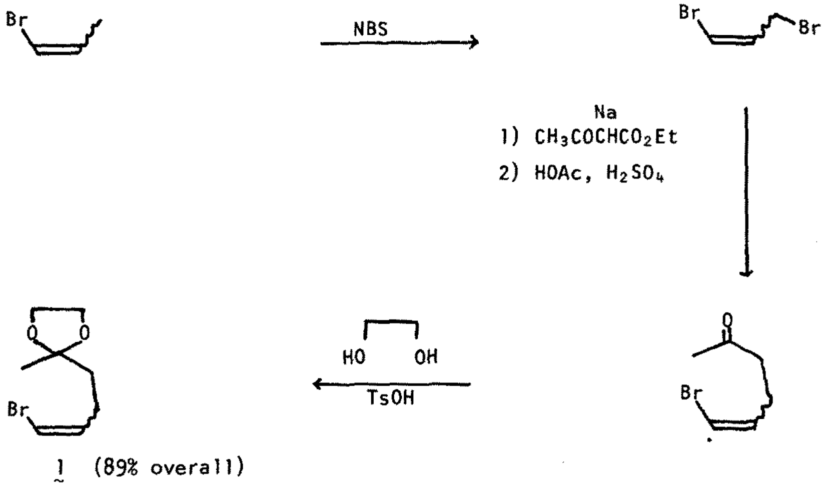
The potential medicinal properties[1] of and the synthetic challenge offered by hydroazulenic lactones have made them the object of much recent work.[2] The most common routes to the hydroazulene carbon framework have been: rearrangement of bicyclic compounds, olefin cyclization and cleavage of tricyclic ring systems.[3] An extension of our ongoing studies of organocuprate β-addition followed by α-alkylation[4] of α,β-enones seemed to offer an alternative approach to the pseudoguaiane system.

Z- and E-1-Hexenyl bromides 1 were readily prepared, equation (1). Condensation of the corresponding vinyl Grignard[5] reagents with 3-ethoxy-2-cyclopentenone,[6] followed by mild hydrolytic work-up, gave dienone 2 as a mixture of isomers in 73% yield after column chromatography. Copper-catalyzed (5% $CuBr{\cdot}S(CH_3)_2$)[7] 1,6-addition of 2-propenylmagnesium bromide to crude or pure dienone 2 yielded 66% of ketal cyclopentenone 3 which was quantitatively hydrolyzed to ketone 4 using oxalic acid in methanol-water at room temperature.

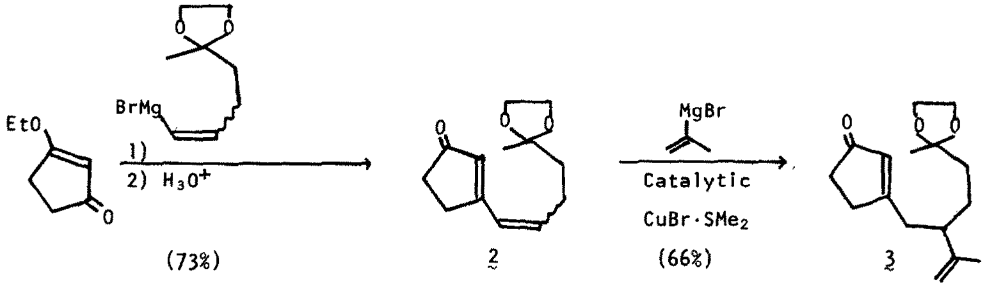
The best results for direct β-addition and subsequent intramolecular enolate cycloalkylation[8] were achieved by adding two equivalents of methylmagnesium chloride and one equivalent of copper bromide-dimethyl sulfide complex to cyclopentenone 4. β-Hydroxy ketone 5 was then dehydrated to give approximately a 2:1 mixture of pseudoguaiane isomers 6a and 6b in 70% yield, equation (3).

Alternatively, an indirect β-addition cycloalkylation route proved to be even more effective. Regiocontrolled formation of silyl enol ether 7 was followed by titanium tetrachloride - mediated intramolecular condensation[9] to give hydroazulenone 6c[10,11] in 55% overall yield from ketal cyclopentenone 3, equation (4).

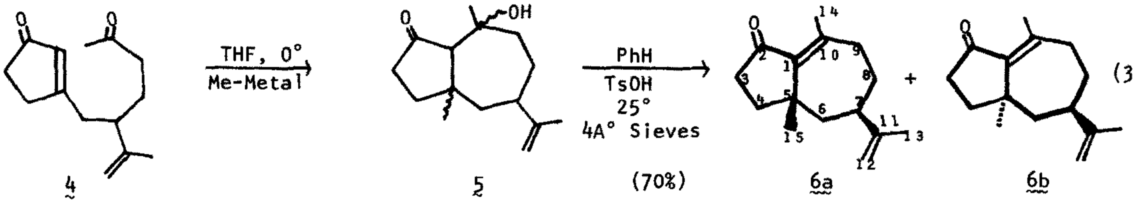
The synthetic procedure, herein described, thus offers a new and efficient route to pseudoguaianes and potentially also to pseudoguaninolides.



(1)

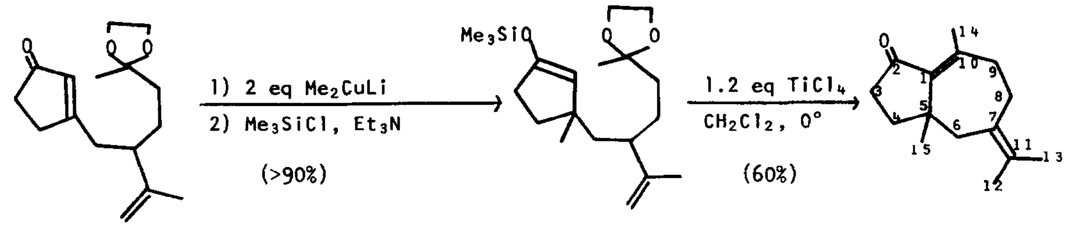


(2)



(3)

| Me-Metal | Yield of 5 |
|---|---|
| 2 eq $Me_2CuLi$ | 10% |
| 2 eq MeMgCl + 10% $CuBr\cdot SMe_2$ | 15% |
| 2 eq MeMgCl + 1 eq $CuBr\cdot SMe_2$ | 25% |



(4)

3 7 6c

Spectral data for 6a, 6b, 6c: ir(CHCl$_3$) 1710 cm$^{-1}$; uv(EtOH) λmax 248 nm, ε = 13,654; high resolution ms calc. for $C_{15}H_{22}O$, 218.167, found 218.171;

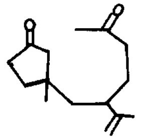
| $^1$H NMR | $CH_3\text{-}\underset{\vert}{C}{=}\underline{CH_2}$ | $C_{10}\text{-}CH_3$ | $\underline{CH_3}\text{-}\underset{\vert}{C}{=}CH_2$ | $C_5\text{-}CH_3$ |
|---|---|---|---|---|
| 6a | 4.64 (m) | 2.21 (s) | 1.69 (s) | 1.16 (s) |
| 6b | 4.64 (m) | 2.25 (s) | 1.69 (s) | 1.21 (s) |
| 6c | -- | 2.18 (s) | 1.56 (s,) $=\!\!\langle^{\underline{CH_3}}_{\underline{CH_3}}$ | 1.19 (s) |

| $^{13}$CNMR | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | $C_6$ | $C_7$ | $C_8$ |
|---|---|---|---|---|---|---|---|---|
| 6a | 138.17s | 208.13s | 47.37t | 36.86t | 44.55s | 31.89t | 39.44d | 37.60t |
| 6b | 138.17s | 208.13s | 47.37t | 35.57t | 44.73s | 32.76t | 42.23d | 37.82t |
| 6c | 138.17s | 208.13s | 49.26t | 36.84t | 44.40s | 34.35t | 147.94s | 39.13t |

| $^{13}$CNMR | $C_9$ | $C_{10}$ | $C_{11}$ | $C_{12}$ | $C_{13}$ | $C_{14}$ | $C_{15}$ |
|---|---|---|---|---|---|---|---|
| 6a | 20.54t | 154.00s | 148.26s | 108.92m | 20.82m | 22.54q | 26.04q |
| 6b | 20.54t | 154.00s | 149.91s | 109.12m | 20.03m | 22.54q | 28.80q |
| 6c | 20.93t | 154.00s | 114.16s | 26.04q | 26.13q | 22.54q | 29.08q |

Acknowledgment. We thank the NIH (CA-12658) for generous financial support.

## References

1. S. M. Kupchan, M. A. Eakin and A. M. Thomas, *J. Med. Chem.*, 14, 1147 (1971).
2. J. A. Marshall and W. F. Huffman, *J. Amer. Chem Soc.*, 92, 6358 (1970); R. A. Kretchmer and W. M. Schafer, *J.Org. Chem.*, 38, 95 (1973); J. A. Marshall and W. R. Snyder, *ibid.*, 40, 1656 (1975); J. A. Marshall and W. R. Snyder, *Syn. Comm.*, 5, 43 (1975); J. A. Marshall and R. H. Ellison, *J. Amer. Chem. Soc.*, 98, 4312 (1976); P. A. Grieco, Y. Ohfune and G. Majetich, *ibid.*, 99, 7393 (1977); P. De Clercq and M. Vandewalle, *J. Org. Chem.*, 42, 3447 (1977); L. A. Macaira, M. Garcia and J. A. Rabi, *J. Org. Chem.*, 42, 4207 (1977).
3. For a review of hydroazulene snythesis see J. A. Marshall, *Synthesis*, 1972, 517.
4. G. H. Posner, J. J. Sterling, C. E. Whitten, C. M. Lentz and D. J. Brunelle, *J. Amer. Chem. Soc.*, 97, 107 (1975) and references cited therein; G. H. Posner and C. M. Lentz, *Tetrahedron Letters*, 1977, 3215; Cf F. Näf, R. Decorzant, and W. Thommen, *Helv. Chim. Acta*, 58, 1808 (1975).
5. Cl. Feugas, *Bull. Soc. Chim. Fr.*, 1963, 2579.
6. W. F. Gannon and H. O. House, "Organic Synthesis," collect. vol. V, Wiley, New York, N. Y., 1973, p. 539.
7. H. O. House, C. Y. Chu, J. M. Wilkins and M. J. Umen, *J. Org. Chem.*, 40, 1460 (1975).
8. In general, the trapping of "copper enolates" with anything other than alkylating agents has resulted in modest yields; see T. Shono, I. Nishiguchi and M. Sasaki, *J. Amer. Chem. Soc.*, 100, 000 (1978) and references cited therein.
9. K. Narasaka, K. Soai and T. Mukaiyama, *Chem. Letters*, 1974, 1223; T. Mukaiyama, K. Banno and K. Narasaka, *J. Amer. Chem. Soc.*, 96, 7503 (1974); K. Narasaka, K. Soai, Y. Aikawa and T. Mukaiyama, *Bull. Chem. Soc. Jap.*, 49, 779 (1976); A. Ishida and T. Mukaiyama, *Chem. Letters*, 1977, 467; for a review of this versatile reagent see T. Mukaiyama, *Agnew. Chem. Int. Ed. Engl.*, 16, 817 (1977).
10. The isolation of enone 6c, rather than the β-alkoxy compound, is not surprising in light of the fact that upon standing in diethyl ether for one week at room temperature 5 dehydrates spontaneously to 6 a & b.
11. Attempted base catalyzed aldol of the dione  failed to produce the desired products.

**(Received in USA 1 June 1978)**