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INTRODUCTION OF ANGULAR METHYL GROUPS VIA RADICAL CYCLIZATION

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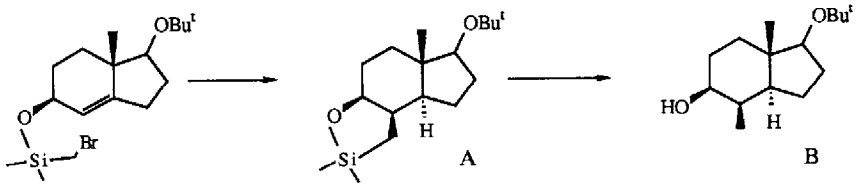
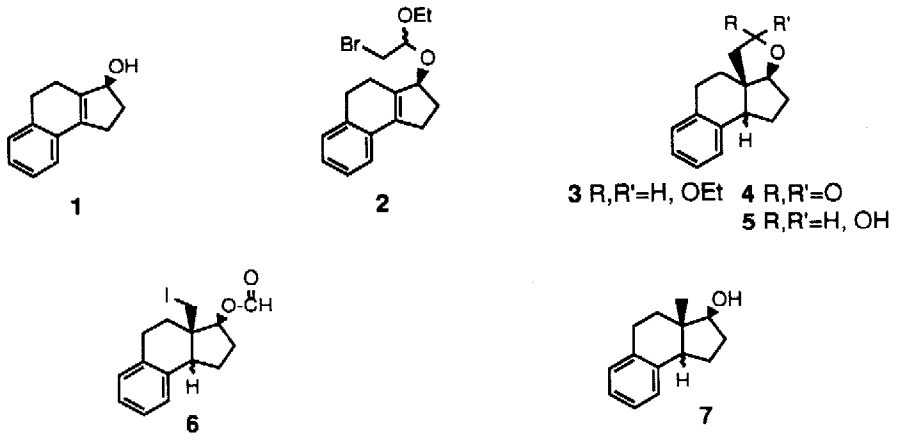
Summary: *Cyclization of radicals formed on chains temporarily tethered to allylic hydroxyl groups in polycyclic systems can be used for the regio-and stereospecific introduction of "angular" methyl groups. As a corollary, the method establishes the stereochemistry of the relevant ring junction.*

Free radical cyclizations involving the temporary connection of a radical precursor to the hydroxyl group of a cyclic allylic alcohol are the basis of a powerful method for the construction of a variety of synthetic targets.[1] We now show that this process, which we have used for the regio- and stereocontrolled insertion of functional carbon chains,[2] can further be used for the controlled introduction of "angular" methyl groups.

The possibility appeared realistic because of the relatively low sensitivity of radical reactions, especially those involving cyclization, to steric hindrance (presumably as a consequence of an early transition state[3]); and because we have previously demonstrated the possibility of generating a methyl group from a cyclic siloxane, as shown in A to B.[4]



As our initial model, we used the readily available tricyclic alcohol **1**[5] which was converted, in the usual manner,[1a] to the mixed bromoacetal **2**.

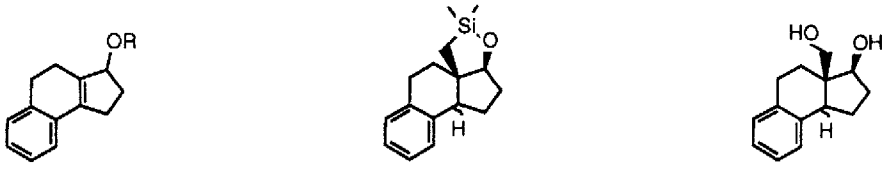


Scheme 1

Cyclization of bromoacetal **2** (Scheme 1) under the usual stoichiometric tin hydride conditions (1.1 equiv Bu_3SnH, 0.1 equiv AIBN, benzene, 0.02M, 80 °C) gave, after Jones oxidation of the crude cyclic acetal **3**, lactone **4** (82%; 3.8:1 mixture by ^1H NMR). Of several different routes explored for the desired formation of "angular" methyl groups from cyclic acetals of type **2**, photochemically-initiated transformation of hemiacetal **5** to the iodomethyl formate **6** (1.1 equiv $PhI(OAc)_2$, 1 equiv I_2, 0.01M in cyclohexane, 40 °C, irradiation with two 100W light bulbs) was found to be the most effective and most generally applicable.[6,7] Lithium aluminum hydride reduction (2.5 equiv) of the crude iodoformate **6** then gave the required alcohol **7**, in 84% overall yield from hemiacetal **5**.

The tricyclic alcohol **7** is a mixture of ring junction isomers which are formed in the initial cyclization leading to **3**. The major isomer, formed in a ratio of nearly 4 to 1, proved to have a cis hydrindane ring fusion, as demonstrated by comparison with well-established values of the ^1H NMR methyl signals for the alcohols[8] (major: δ 1.04; minor: δ 0. 65) and the corresponding ketones[9] (major: δ 1.12; minor: δ 0.72).

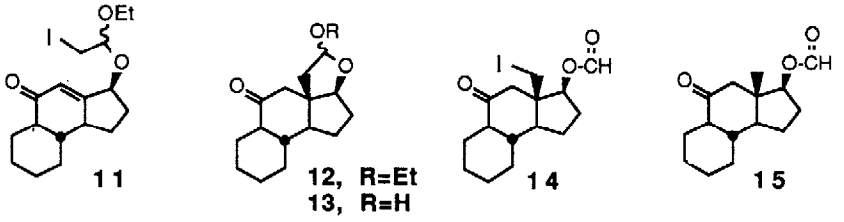
Introduction of an angular methyl starting with the tricyclic allylic alcohol **1** was also studied using a silicon-containing tether.[4,10] Treatment of silyl ether **8** (Scheme 2) with stoichiometric tin hydride, followed by oxidative desilylation[11,4] of the crude siloxane **9** resulted in the formation of diol **10** (91%) along with some recovered **1** (6%). Alternatively, the crude cyclic siloxane **9** could be reductively desilylated, in DMF,[12] (10 equiv $Bu_4N^+F^-$, 5:1 v/v DMF/THF, 60 °C) to give the same alcohols **7** (84%) as were prepared using the acetal tether. A similar (3.7:1) mixture of isomers was obtained, again in favor of the *cis*-fused isomers.



8, R = $Si(Me)_2CH_2Br$ **9** **10**

Scheme 2

As a further test of the generality of these procedures, iodoacetal **11** (Scheme 3) was prepared[2a] from the relevant hydroxyenone[13] and subjected to the stoichiometric tin hydride conditions[2a] to produce cyclic acetal **12** (86%). The corresponding lactol **13** was photolyzed, as before, to give iodoformate **14** (71%) which was then reduced under the catalytic tin hydride conditions[2a] (0.1 equiv Bu_3SnCl, 2 equiv $NaBH_3CN$, 0.3 equiv AIBN, *tert* BuOH, 0.02M, 83 °C) to give ketoformate **15**[14] (42% from **12**). (The stereochemical assignment was confirmed by the position of the methyl group in the ^1H NMR spectra at δ 0.76, in agreement with expectations[15,16].



11 **12, R=Et** **13, R=H** **14** **15**

Scheme 3

We conclude that the tethered radical cyclization method can lead to the stereocontrolled introduction of "angular" methyl groups in polycyclic systems. A methyl group is thus introduced, at the proximal olefinic carbon of an allylic alcohol, stereospecifically cis to the controlling hydroxyl. An important corollary is that the stereochemistry of the newly established ring junction can be made either cis or trans by the proper choice of the allylic hydroxyl stereochemistry (cf. **11** to **15**).

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

References and Notes

1) See, for instance, (a) G. Stork, R. Mook, Jr., S. A. Biller and S. D. Rychnovsky, *J. Am. Chem. Soc.*, **105**, 5510 (1983); (b) G. Stork and P. M. Sher, *J. Am. Chem. Soc.*, **105**, 6765 (1983); (c) G. Stork, in "Selectivity, a Goal for Synthetic Efficiency", S. W. Bartman and B. M. Trost, Ed.; Verlag Chemie: Basel, 1984, pp. 281-299.

(2) (a) G. Stork, and P. M. Sher, *J. Am. Chem. Soc.*, **108,** 303 (1986); (b) G. Stork, P. M. Sher and H. L. Chen, *J. Am. Chem. Soc.*, **108,** 6384 (1986); (c) G. Stork, *Bull. Chem. Soc. Japan*, **61,** 149 (1988).

(3) See: A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron*, **41,** 3925 (1985); D. C. Spellmeyer and K. N. Houk, *J. Org. Chem.*, **52,** 959 (1987).

(4) G. Stork and M. Sofia, *J. Am. Chem. Soc.*, **108**, 6828 (1986). G. Stork and M. Kahn, *J. Am. Chem. Soc.* 107, 500 (1985).

(5) Made by borohydride reduction of the corresponding ketone: W. S. Johnson, H. C. E. Johnson and J. W. Petersen, *J. Am. Chem. Soc.*, **67,** 1360 (1945).

(6) This procedure is based on the method used by Suarez et al. (R. Freire, J. J. Marrero, M. S. Rodriguez and E. Suarez, *Tetrahedron Lett.*, **27,** 383 (1986)) for the construction of macrocyclic lactones from hemiacetals. This procedure gave considerably better yields with our molecules than the closely related method of H. Suginome and S. Yamada, *Tetrahedron Lett.*, **26,** 3715 (1985).

(7) Other methods, used with variable but generally unsatisfactory results, include the decarbonylation of hemiacetals such as **3** with the Wilkinson catalyst (cf. J. Tsuji in "*Organic Synthesis* via Metal Carbonyls", I. Wender, Ed.; Wiley; New York, 1977; Vol. 2, p. 595 *ff.*; M. D. Meyer and L. I. Kruse, *J. Org. Chem.*, **49,** 3195 (1984)).

(8) A. B. Turner and S. Kerr, *J. Chem. Soc., Perkin Trans.I,* 322 (1979).

(9) V. I. Sladkov, V. F. Shner and N. N. Suvorov, *Zhur. Org. Khim.*, *8,* 1549 (1972).

(10) H. Nishimaya, T. Kitajima, M. Matsumoto and K. Itoh, *J. Org. Chem.*, **49,** 2298 (1984).

(11) K. Tamao, N. Ishida, T. Tanaka, and M. Kumada, *Organometallics*, **2,** 1694 (1983).

(12) Unpublished work with P. F. Keitz in this Laboratory.

(13) The starting 17- β-hydroxyenone used to make **11** was prepared by peracid oxidation (compare D. M. Kirk and J. M. Wiles, *Chem. Commun.*, 1015 (1970)) of the enol acetate of the tricyclic enone made by reaction of the pyrrolidine enamine of cyclopentanone with acetylcyclohexene (cf. L. H. Hellberg and M. F. Stough,III, *Acta Chem. Scand.*, **21**, 1368 (1967)). This oxidation gave the β-hydroxyenone corresponding to **11** as the major isomer together with its hydroxyl epimer. The best results (>20:1 in favor of the β-epimer; 70% yield) were obtained with m-chloroperbenzoic acid in 95% aq. ether (0 °C to room temperature). The hydroxyenone used here was made by an earlier procedure, due to D. H. Sherman in this Laboratory, using 95% ethanol as solvent in the peracid oxidation. This had given a lower ratio (7.5 :1) in favor of the required β-epimer corresponding to **11.** The stereochemistry of the major, 17-β, epimer was ascertained by X-ray crystallography. We thank Professor S. D. Darling, University of Akron, for this determination.

(14) Reduction of **14** with lithium aluminum hydride, under the conditions which successfully effected the transformation of **6** to **7,** formed a tetrahydrofuran, in this particular case, by cyclization of the resulting cyclohexanol with the iodomethyl group.

(15) N. S. Bhacca and D. H. Williams, "*Applications of NMR Spectroscopy in Organic Chemistry: Illustrations from the Steroid Field*", Holden-Day, Inc.; San Francisco, 1964; chapter 2.

(16) The radical cyclizations described in this report are undoubtedly facilitated by the styrene or enone nature of the acceptor olefins. This is not required, however, as was shown several years ago by Dr. P. Fludzinski in this Laboratory, starting with the bromoacetal of the indenol corresponding to **2.** This cyclization (Bu_3SnH, 76% yield) gives the two possible stereochemistries at the ring junction of the resulting hydrindanes (1.6:1). We have now established the cis configuration of the major product by conversion to the known relevant cis and trans methylhydrindanones.

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