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STEREOSELECTIVE SYNTHESIS OF (±) - LAURENE

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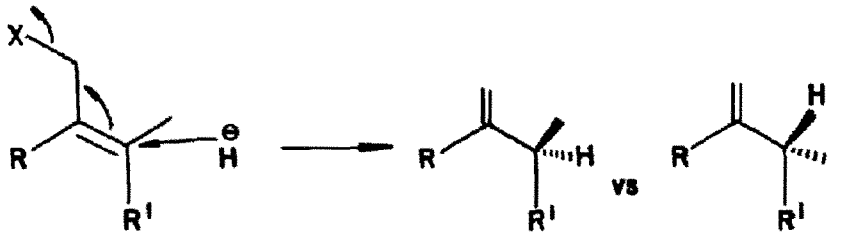
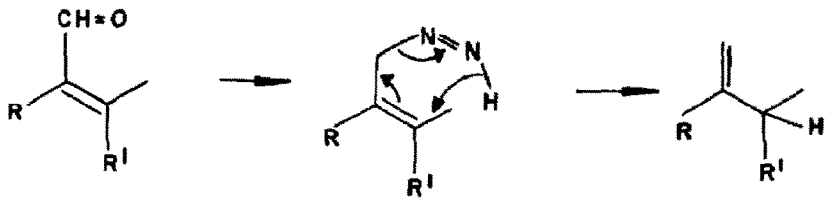
SUMMARY: Reduction of an unsymmetrically substituted unsaturated aldehyde by way of the corresponding tosylhydrazone is shown to proceed stereoselectively.

A common problem in synthetic chemistry is control of asymmetry adjacent to an sp^2 center. When the outcome desired is thermodynamically preferred, a Wittig reaction on the corresponding ketone offers a reasonable solution. When the outcome desired is less favored thermodynamically, or when there is no clear preference, this approach is not necessarily satisfactory.[1a] We report a new approach to this problem, culminating in a stereoselective synthesis of the sesquiterpene hydrocarbon laurene 4.[1]

A solution to this problem should combine kinetic generation of asymmetry with simultaneous formation of the carbon-carbon double bond. Conceptually, this can be illustrated by SN-2' attack of hydride on an allylic leaving group.



The key to this approach is control of the newly-formed asymmetric center. To achieve such control, a rigid transition state for hydride delivery would be desirable. It would also be necessary to insure regioselective hydride delivery. These criteria seemed best fulfilled by reduction of the tosylhydrazone[2] of the corresponding unsaturated aldehyde.[3]



We have therefore embarked on a program to investigate steric and stereoelectronic control elements in tl reaction.

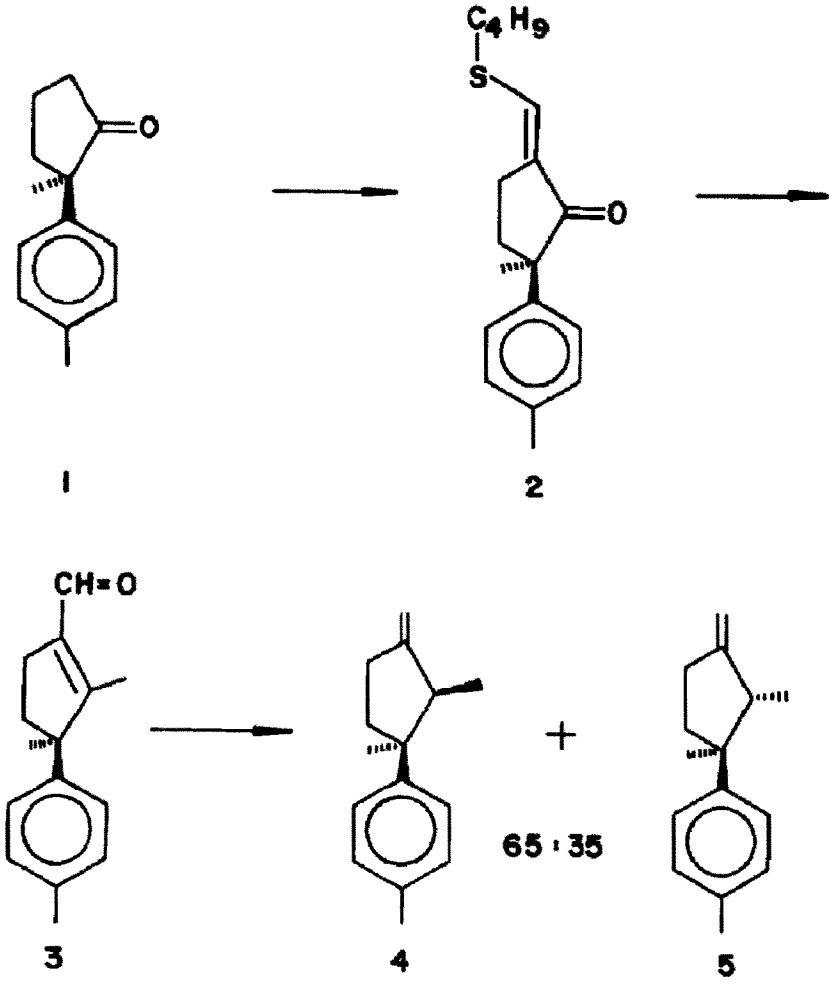
The present work focuses on the sensitivity of this reaction to steric hindrance. In designing a substra to test such sensitivity, it would be necessary to eliminate stereoelectronic influences on the course of t reaction. Thus, the starting olefin should either be acyclic or, preferably, to minimize bond rotations in t transition state, incorporated in a five-membered ring. Further, while the transition state for hydri delivery across one face of the olefin should involve more steric hindrance than that for delivery across t other face, this hindrance should not be so severe that sensitivity of the reaction to minimal ste differences could not be assessed. Finally, the resultant olefins should be different enough that stere chemical analysis of the outcome of the reaction would be straightforward.

Aldehyde 3 fulfills all of these criteria. Models indicated that steric interactions with the aryl gro while relatively slight, should be more significant than steric interactions with the methyl group. Thus, would be possible to assess the impact of minimal steric bias on the course of the reaction. Significant both products of the reaction were known,[1a] and easily differentiated.

Aldehyde 3 was readily prepared from ketone 1, previously employed by McMurry[1a] in a synthesis laurene. Butylthiomethylenation[5] led to 2 (60%),[6] which on treatment with methyl lithium and hydrolys following the procedure of Bernstein,[7] gave the desired 3 (42%)[6]. In the event, catecholborane reduction[2] the tosylhydrazone (93% from 3)[6] followed by treatment with $NaOAc \cdot 3H_2O$ (RT, 18 hrs) gave a hydrocarb mixture (68%). This mixture showed two components on GC(6 ft 1/8" 3% OV-17, 25 ml/min, 125°, 4.1 and min) in a ratio of 65:35. These were separated by preparative GC, and identified respectively as laurene[8] a epilaurene[9].

We have briefly explored other reducing systems. $NaBH_3CN$(DMF-sulfolane, 100°)[2b] was inferior, givi a 30% yield with a 55:45 ratio of laurene to epilaurene. $NaBH_4$/HOAc[2c] was better (66%, 62:38). Final reasoning that the intramolecular hydride delivery should be more selective at lower temperature, we tri $NaBH_4$ in 1:1 CH_2Cl_2/HOAc at -10°(Dry Ice/brine). The reaction mixture was allowed to come to RT ove hr, by which time N_2 evolution seemed to be complete. The reaction mixture was stirred at RT overnig then worked up to give a 61% yield of hydrocarbon, with a laurene to epilaurene ratio of 66:34. It is lik that other hydride reducing systems at still lower temperatures would be even more selective.

SCHEME



1 2 3 4 5

It is apparent that the tosylhydrazone reduction procedure does proceed with a fair degree of selectivity, in what was designed to be a minimally biased system. It is to be expected that where the bias is more pronounced, stereoselectivity should be greater.

To make this approach to controlling asymmetry adjacent to an sp^2 center more general, it will be necessary to assess stereoelectronic influences on the stereochemical outcome of this reaction. In this case, the starting olefin should be incorporated in a rigid six-membered ring. Work in this direction is currently in progress.

Acknowledgments: We are appreciative of stimulating discussions with Professor George Kabalka. T investigation was supported by the National Institutes of Health, GM 15431. We acknowledge support fr Biomedical Research Support Grant RR-05424 for MS and NMR instrumentation.

REFERENCES AND NOTES

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3. It should be noted that for unsaturated ketones, the chirality of the newly formed asymmetric center dictated by the chirality of the initial hydride reduction of the tosylhydrazone[4].

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6. All new compounds were homogeneous by TLC and gave NMR, IR and mass spectra consistent with th assigned structure.

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8. Laurene[1] H NMR: 0.69, d, J=7, 3H; 1.28, S, 3H; 2.31, S, 3H; 4.87, bs, 2H.

9. Epilaurene[1] H NMR: 0.93, d, J=6, 3H; 1.08, S, 3H; 2.33, S, 3H; 4.82, bs, 1H; 4.90, bs, 1H.

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