

SYNTHESIS OF SPIRO-SESQUITERPENES IN THE VETIVANE SERIES VIA

AN AZA-CLAISEN REARRANGEMENT

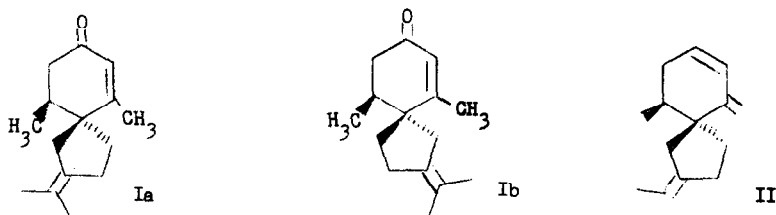
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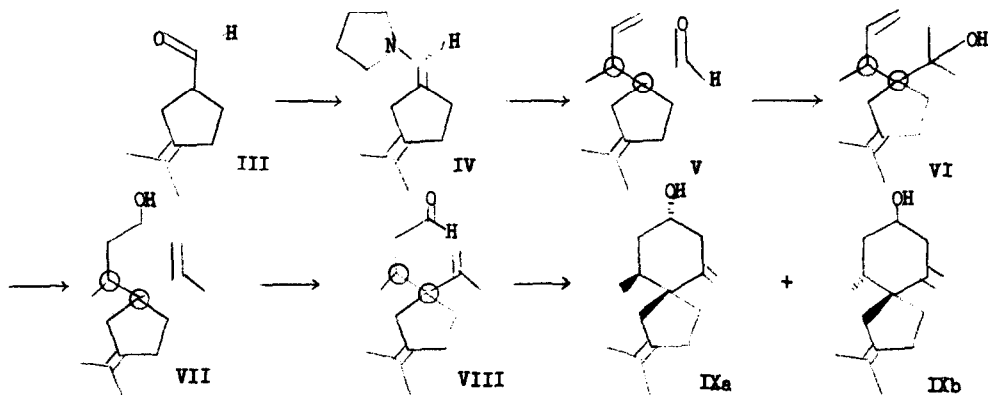
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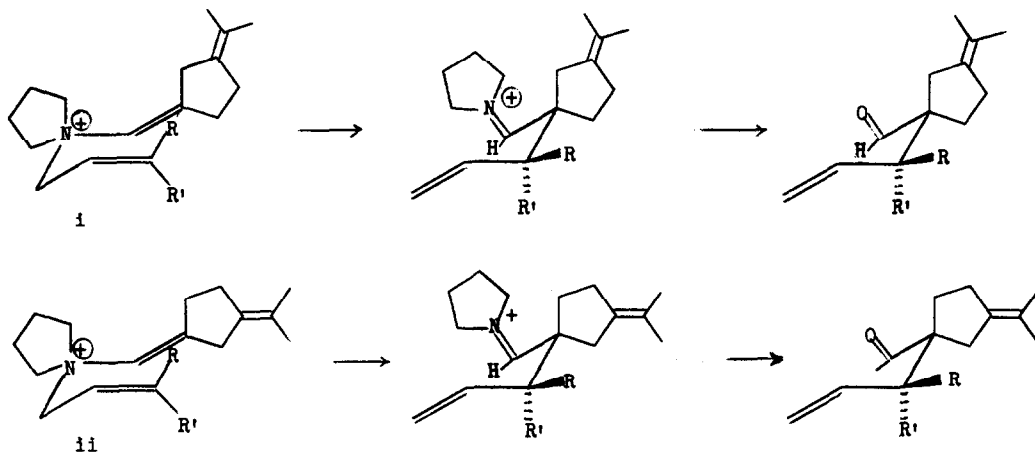
We wish to report a version of the aza-Claisen rearrangement¹ which should prove useful in the preparation of diastereomeric spiro compounds. Specifically, we have applied this method in the total synthesis of spiro-sesquiterpenes (\pm) β -vetivone (Ia),^{2a} (\pm) 10-epi- β -vetivone^{2b} (Ib), and (\pm) β -vetispirene³ (II).



Camphoceanic aldehyde⁴ (III) [b.p. 88-92° at 13 mm; nmr 1.60 (6H), 9.40 (1H, d, $J = 1.5$ Hz)], obtained in 86% yield from camphoceanic nitrile,⁵ by reduction with diisobutyl aluminum hydride at 0°, was converted to the trisubstituted pyrrolidine enamine IV [97% yield, b.p. 78-80° at 0.1 mm; nmr 1.61 (6H), 5.70 (1H)].

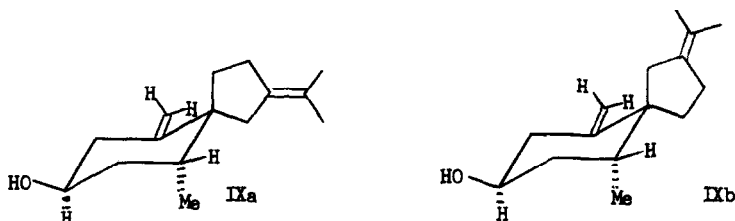


Enamine IV, when reacted with pure *trans*-crotyl bromide (acetonitrile, 80°, followed by buffered acetate hydrolysis), furnished in 75% yield a 55:45 of diastereomers (250 MHz nmr) of the alkylated aldehyde V [b.p. 68-69° at 0.1 mm; nmr, major 1.015 (doublet, $J = 7.00$ Hz), minor 1.025 (doublet, $J = 7.00$ Hz), 9.428 (1H)]. Alternatively, when the enamine was treated with *cis*-crotyl bromide,⁶ the diastereomeric ratio was reversed (45:55). These experiments suggest that the 3,3 sigmatropic rearrangement of quaternary salts i and ii ($R = H$, $R' = Me$ or $R = Me$, $R' = H$) is a highly stereospecific reaction.

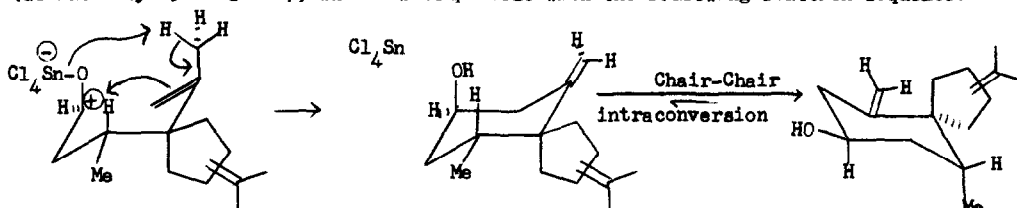


Aldehyde V, (derived from *trans*-crotyl bromide) was converted to the corresponding tertiary carbinol VI by (a) treatment with methyl lithium, (b) oxidation to the corresponding methyl ketone (with *N*-chloro succinimide, dimethyl sulfide and triethyl amine⁷ at -20°), and (c) repeated treatment with methyl lithium, (overall yield 93%). Conversion of VI to the isomeric primary alcohol VII was effected by (a) selective hydroboration with disiamyl borane followed by oxidation with basic hydrogen peroxide, (b) protection of the primary alcohol as its acetate, (c) dehydration of the tertiary alcohol function with thionyl chloride in pyridine at 0° and (d) removal of the acetate with lithium aluminum hydride (overall yield 57%, b.p. 105-115° at 0.1 mm).

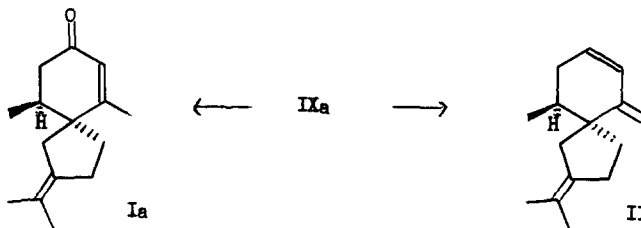
The alcohol VII was smoothly oxidized⁷ in 96% yield to the corresponding aldehyde VIII (b.p. 110-112° at 0.1 mm). The aldehyde VIII undergoes an acid catalyzed Prins⁸ cyclization to a separable mixture of diastereomeric spiro-alcohols IXa and IXb⁹ when exposed to a catalytic amount of stannic chloride¹⁰ in methylene chloride for 90 seconds (90% yield).



Although there was formally the possibility of the formation of four diastereomeric *dl* pairs in the acid-catalyzed Prins reaction, isomer IXa and IXb accounted for over 97% of the reaction mixture. Both isomers possessed an equatorial alcohol function and an axial methyl group (as shown by 250 MHz nmr), which is compatible with the following reaction sequence:



The pure homoallylic alcohol IXa was oxidized (using Doering's modification of the Moffat oxidation)¹¹ in 90% yield to afford racemic Ia whose physical properties (ir, 250 MHz nmr,¹² and high resolution mass spectra, and glc retention time) are identical to those of an authentic sample of (+) β -vetivone. Similarly (+) 10-*epi*- β -vetivone¹ was obtained from IXb.



When the mesylate of homoallylic alcohol IXa was refluxed in pyridine for two hours, a diene was produced in 90% yield which was shown to be (+) β -vetispiene¹³ by comparison with a sample of natural levorotatory material.¹⁴

This route to diastereomers has a potential use in other applications especially when enamines of known geometry can be isolated in pure form, and we are investigating this possibility.

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(b) P. M. McCurry Jr., R. K. Singh and S. Link, Tetrahedron Letters, 1155 (1973).
3. Also referred to as β -isovetivenene, see footnote 13.
4. All new compounds gave satisfactory elemental and/or mass spectral data and compatible ir and nmr (250 MHz) spectra.
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8. A thermal Prins reaction was also effected on attempted Preparative glc of VIII.
9. Compound IXa is a solid, m.p. 101-104^o, while compound IXb is a liquid.
10. J. A. Marshall, N. H. Andersen and P. C. Johnson, J. Org. Chem., 35, 186 (1970).
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12. For 250 MHz nmr Spectra of (+) β -vetivone and (+) 10-epi- β -vetivone, see reference 2b.
13. N. H. Andersen, M. S. Falcone and D. D. Syrdal, Tetrahedron Letters, 1759 (1970).
14. A sample of natural β -vetispiene was kindly supplied by Professor N. H. Andersen.