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FURTHER STUDIES ON THE PINACOL COUPLING REACTION

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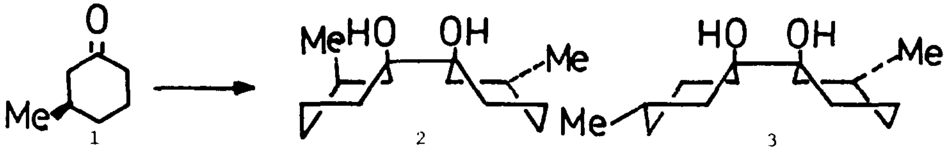
ABSTRACT: The pinacol coupling of R(+)3-methylcyclohexanone gives a product distribution <u>dependent on the mode of coupling</u>. Similar changes in product composition are also seen in the coupling of 4-methylcyclohexanone and in the mixed coupling of 3-methylcyclohexanone with cyclohexanone. In <u>all cases studied</u>, the [Al-Hg] method results in products having an axial methyl group. An X-ray structure of a product containing two axial methyl groups is presented.

In 1978 a report was published that the [Al-Hg]-mediated reductive coupling of R(+)-3-methylcyclohexanone, **(1)**, gave **2** as the sole product[1]. Our subsequent observation that **3** was the major product from the reduced titanium-mediated coupling[2] of **1** forced us to reexamine several aspects of the coupling reaction[3]. As part of this reexamination, we repeated the [Al-Hg] work, and found what appeared to be a single product. The product was homogeneous by packed GLC and its proton-NMR spectrum exhibited two cleanly-resolved methyl doublets (J = 6 Hz) centered at 0.85 and 1.10 ppm. These data supported the assignment of **2** as the product from this reaction.



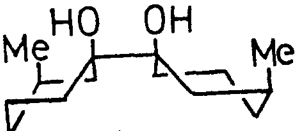
1 2 3

As part of our continuing program on subtle factors controlling the course of pinacol rearrangements[4], we decided to investigate the fragmentation patterns of substituted 1,2-diols. With the recent acquisition of new mass spectrometers and the use of capillary chromatography interfaced with the instruments[5], we injected a sample of our "pure" **2** onto a 30 m capillary column. To our surprise we found three isomeric products. The "pure" **3** gave two isomeric products. Since packed GLC did not separate these isomers, we looked for other chromatographic methods. Flash chromatography [silica gel; petroleum ether/ ether (1:1)] monitored by capillary chromatography, allowed us to separate pure samples of each isomer. The results of this work (three independent coupling reactions) are summarized in Table I.

Table I
Products with Physical and Spectroscopic Data for the Coupling Reaction[4]

1 **Reaction Conditions**	**2**	**+**	**3**	**+**	**4**
[Al-Hg]	52.7		16.4		30.9
[Ti]	17.3		82.7		---

Compound	**mp(°C)**	**^{1}-H-NMR (Methyl)**
2	70-71	1.10 ppm 0.85 ppm
3	76-77	0.85 ppm
4	100	1.10 ppm



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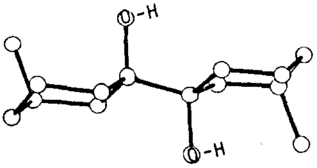


Although the NMR chemical shift data were in accord with a diaxial product, we unambiguously determined the structure of **4** by way of an X-ray crystal structure. The computer-generated "ball-and-stick" model for this compound shows that there is no distortion of either cyclohexane ring, and that the methyl groups are truly axially oriented.

Although these new results are quantitatively different from those of our earlier discussion, we are left with the same qualitative observation: the coupling processes must be different. However, a question had to be answered:

was the result from the reaction of 3-methylcyclohexanone an exception to a general rule or was this a first indication of a general trend? We thus undertook an examination of the reductive coupling of 4-methylcyclohexanone. Products from this reaction are shown below, and the results of this study are presented in Table II.

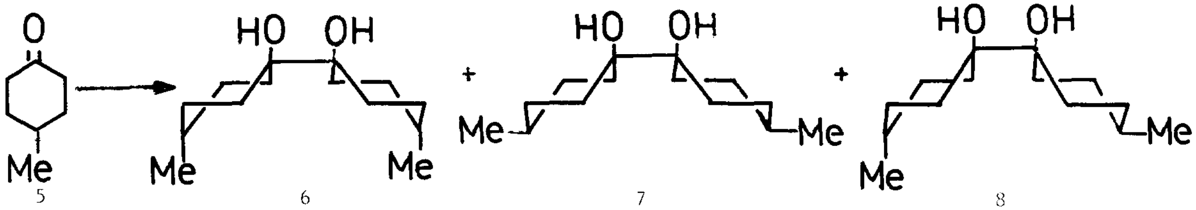
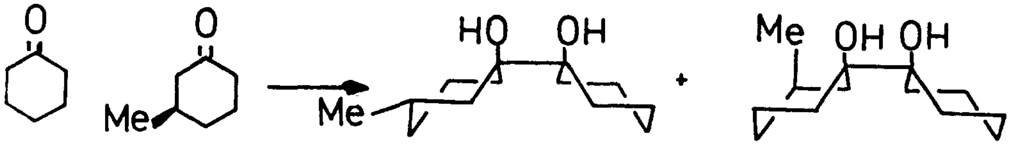

5 6 7 8

Table II
The Reductive Coupling of 4-Methylcyclohexanone

5	Reaction Conditions	6	+	7	+	8
	mp(^{o}C)	119-120		93-94		104-106
	[Al-Hg]	43		13		44
	[Ti]	4		63		33

Lastly we examined a mixed coupling reaction-- that of R(+)-3-methylcyclohexanone with cyclohexanone. Although the expected self-coupling of **1** and **9** was observed, we show here <u>only</u> the mixed coupling products .


9 1 10 11

	10	11
mp(^{o}C)	90-91	86-89
[Al-Hg]	41	59
[Ti]	91	9

From these combined data we see that in all cases the titanium-mediated coupling gives different product compositions than found with the traditional Al-Hg procedure. And, when the [Al-Hg] coupling is carried out a major component of the product mixture will have axial methyl groups. These observations suggest the possibility of new synthetic potentials for the use of the pinacol *coupling reaction to generate compounds of unique and predictable* stereochemistry.

Current work in our laboratory is being directed towards trying to understand the origins of these differences in the coupling processes.

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2. E.J. Corey, R.L. Danheiser and S. Chandrasekaran, **J. Org. Chem.**, (1976), 41, 260.

3. B.P. Mundy, Y. Kim, T. Dolph and R.J. Warnet, **J. Org. Chem.**, (1982), 47, 1657.

4. B.P. Mundy and R. Srinivasa, **Tetrahedron Letters**, (1979), 2671 and earlier papers cited.

5. Using a VG model MM16 mass spectrometer with a 15 m SE-30 capillary column, separation of the isomeric pinacols was not achieved. However, the high resolution VG model 7070 E-HF with a 30 m DB5 capillary column allowed us clean and complete separation of products, quantitative integration of product ratios, and HRMS molecular weights. From these data alone we were assured of having isomeric pinacols. The proton NMR spectra unambiguously assigned the methyl group orientations.

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