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THE SYNTHESIS OF OPTICALLY ACTIVE α-DEUTERIOKETONES

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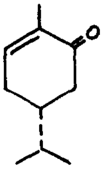
Several research groups have succeeded in synthesizing optically active β-deuteriocycloalkanones which owe their chirality to the deuterium substituent alone[1,2]. The rotational contribution of this substituent was found, in most cases[3], to be anti-octant (dissignate[4]). The first synthesis of optically active α-deuterio (otherwise achiral)- cycloalkanones: specifically the conformationally fixed cyclohexanones 4d and 4e has very recently been reported by Sundararaman and Djerassi[2]. Here also, dissignate behavior was found for the α-axial deuterium of 4d and, considerably diminished in magnitude, for the equatorial α-deuterium of 4e. We wish to report an alternative synthesis of 4d as well as the synthesis of the α,α-dideuterio-cyclohexanone 6b. The optical rotatory properties of these products *(vide infra)* confirm the strong dissignate contribution of an α-axial deuterium substituent.



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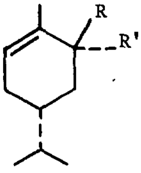
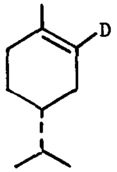


2a,R=D;R'=OH d,R=D;R'=Cl
b,R=OH;R'=D e,R=D;R'=H
c,R=Cl;R'=D f,R=H;R'=D



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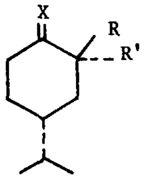
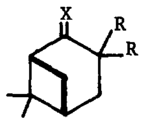
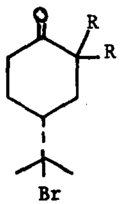


4a,X=CH$_2$,R=D,R'=H
b,X=CH$_2$,R=H,R'=D
c,X=OH,CH$_2$OH;R,R'=H,D
d,X=O,R=D,R'=H
e,X=O,R=H,R'=D
f,X=O,R=R'=H



5a,X=CH$_2$,R=H
b,X=O,R=H
c,X=O,R=D



6a R=H
b R=D

Catalytic hydrogentation of (-)-carvone[5] with tris(triphenylphosphine)chlororhodium gave R-(-)-carvotanacetone(1) ($[\alpha]_D^{22}$ - 56.7° neat) which underwent stereoselective reduction[6] with $LiAlD_4$ to provide a mixture of the deuterated *cis*- and *trans*-carvotanacetols 2a and 2b 96:4 ratio by GLC). The mixture of allylic alcohols, when treated sequentially with molar equivalents of n-BuLi, tosyl chloride, and LiCl according to the published procedure,[7] was converted, largely with inversion,[8] to a mixture of the epimeric allylic chlorides 2c and 2d (84:16 ratio). The absence of rearranged allylic chlorides was indicated by the complete lack of proton absorption in the region for a $-\underset{|}{C}=\underset{|}{C}-CH(Cl)-$ proton (δ 4.4- δ 4.6). Reduction of the allylic chloride mixture with $LiAlH_4$ gave a mixture of the (4S)-6-deuterio-p-menth-1-enes 2e and 2f along with (R)-2-deuterio-p-menth-1-ene(3), formed by an S_N2' process. The latter product was present to the extent of 10% as estimated (a) from a proton nmr spectrum of the total product, by integration of the vinyl proton region and (b) by comparison of the absolute magnitude of the specific rotation of this mixture ($[\alpha]_D$-71.9° ether) with that of authentic (+)-p-menth-1-ene ($[\alpha]_D$ + 91.4 ether). The 2e and 2f components of this mixture may be assumed to arise by direct displacement with inversion from 2c and 2d, respectively. Therefore, their percentages should lie between 74% 2e, 16% 2f and 84% 2e, 6% 2f depending on the relative extent that 2c and 2d contribute to the production of 3. Irradiation[9] of this mixture of monodeuterated p-menth-1-enes resulted in complete isomerization of the double bond to the exocyclic position, providing a mixture of (4R)-2-deuterio-p-menth-1(7)-enes 4a and 4b.[10] Since 10% of this product must arise from 3 in a reaction of unknown stereo-selectivity, the product composition should lie between 74% 4a, 26% 4b and 94% 4a, 6% 4b. Hydroxylation of (4a + 4b) using Sharpless' procedure[11] produced a mixture of diastereomeric glycols (4c), m.p. 64-67° after crystallization from hexane. Aqueous periodic acid oxidized 4c to a mixture (7% d_0, 93% d_1) of (2S, 4R)- and (2R, 4R)- 2-deuterio-4-isopropyl-cyclohexanones 4d and 4e, respectively, admixed with undeuterated 4-isopropylcyclohexanone (4f). The partial loss of deuterium in the final step probably occurs largely at the expense of 4d since it is (a) the major isomer and (b) the one in which the α-deuterium substituent is axial. Taking this into account, the final product should contain between 67% and 87% of 4d, the remainder being 4e and 4f. The optical rotatory dispersion (ORD) spectrum of this product (Figure 1) exhibits a negative Cotton effect centered at 290 nm with a molecular amplitude,[12] a = -1.75; pure 4d should, then give a value for a between -2.01 and -2.60.[13] Repetition of this sequence of reactions, but using $LiAlH_4$ instead of $LiAlD_4$ for the reduction of carvotanacetone led to a sample of 4-isopropylcyclohexanone which was devoid of measurable optical activity from 240-600 nm. An octant projection of 4d, for the chair form in which the isopropyl group is equatorial, places the deuterium substituent in the lower right back (normally +) octant. The strong negative Cotton effect observed for 4d establishes the dissignate behavior of an axial deuterium substitutent α to a cyclohexanone carbonyl.

A second cyclohexanone derivative whose chirality is due only to α-deuterium substitution was synthesized from (1S,5S)-(+)-nopinone (5b) ($[\alpha]_D^{25}$ + 30.6 $CHCl_3$) obtained by oxidation of (-)-β-pinene.[5] Deuterium exchange of 5b with K_2CO_3 in D_2O produced the dideuterated derivative 5c (4.7% d_1, 95.3% d_2). Opening of the four-membered ring of 5c was accomplished with BBr_3 in CH_2Cl_2 at -70° followed by the addition of pyridine in methanol at the same temperature. Aqueous work-up then gave (R)-2,2-dideuterio-4-(2-bromo-2-propyl)-cyclohexanone (6b)[14] (20.3% d_1, 79.7% d_2), m.p. 83-85°. The ORD spectrum of this sample (Figure 2) exhibits a negative Cotton effect at 295 nm with a = -3.17 (for isotopically pure 6b, the absolute value of a could be 25% higher). The corresponding product from undeuterated nopinone was devoid of measurable optical activity. An octant projection of 6b is similar to that of 4d except for the presence of an equatorial deuterium substitutent near to a boundary plane which presumably makes only a minor contribution[2] to the Cotton effect. Thus, the α-axial deuterium substituents of 6b and 4d both make dissignate Cotton effect contributions and give rise to molecular amplitudes in the range -2.0 to -4.0.

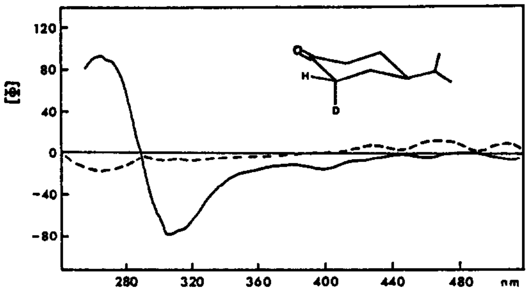


Figure 1. ORD spectra in dioxane at 25°; solid line, 4d; dashed line 4f.

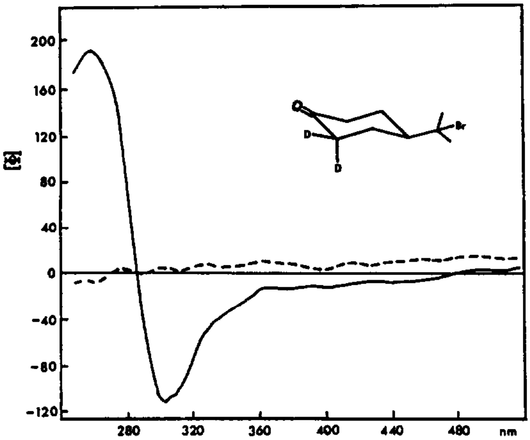


Figure 2. ORD spectra in dioxane at 25°; solid line, 6b; dashed line, 6a.

The above results find direct application to recent work on enantioselective hydrogen isotope exchange of prochiral α-hydrogen substituents of cycloalkanones. Hine and Li[15] have studied protium incorporation into cyclopentanone-2,2,5,5-d_4 under the influence of an optically active base catalyst. After an appropriate reaction time, the isotopic mixture gave a positive Cotton effect (290 nm, a = +2.0) and was found by mass spectral data to consist largely of cyclopentanone -2,5-d_2. The 2R,5R configuration assigned to this product on the assumption of a dissignate contribution from α-deuterium is confirmed by the present work.[16]

References and Notes

1. J. W. Simek, D. L. Mattern, and C. Djerassi, Tetrahedron Letters, 3671 (1975); D. A. Lightner, T. C. Chang, and J. Horwitz, *ibid.*, 3019 (1977) [correction: 696 (1978)]; H. Numan and H. Wynberg, *J. Org. Chem.*, **43**, 2232 (1978); C. Djerassi, C. L. Van Antwerp, and P. Sundararaman, Tetrahedron Letters, 535 (1978); S. F. Lee, G. Barth, K. Kieslich, and C. Djerassi, J. Am. Chem. Soc., **100**, 3965 (1978).
2. P. Sundararaman and C. Djerassi, *Tetrahedron Letters*, 2457 (1978).
3. One exception is that of the β, axial deuterium in the 4-t-butylcyclohexanone series described by Sundararaman and Djerassi[2] which exhibits a small consignate contribution.
4. W. Klyne and D. N. Kirk, *ibid.*, 1483 (1973).
5. The starting materials used in this work are of established absolute configuration: W. Klyne and J. Buckingham, Atlas of Stereochemistry, Chapman and Hall, London, 1974, pp. 81 and 84.
6. H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).
7. G. Stork, P. A. Grieco, and M. Gregson, *Tetrahedron Letters.*, 1393 (1969).
8. The sterochemistry of the major allylic halide was deduced from the proton NMR spectrum of the corresponding undeuterated mixture which included a signal of nearly 1H intensity for -CHCl at δ 4.48 with $W_{1/2}$ 6 Hz.
9. P. J. Kropp and H. J. Kraus, J. Am. Chem. Soc., **89**, 5199 (1967). The photochemical reaction was conducted in ether containing phenol as photosensitizer and proton source. Our thanks are due to Professor Kropp for advice on reaction conditions and to Dr. Colin Pitt for calling our attention to the above reference.
10. One might conjecture that the photochemical reaction conditions could allow partial equilibration between the enantiomeric p-menth-1-enes and, therefore, partial loss of optical activity. This is probably not the case, since such a process would also entail loss of deuterium whereas mass spectral analysis of the product (4a + 4b) shows that essentially all of the deuterium is retained (1% d_0, 99% d_1).
11. K. B. Sharpless and K. Akashi, *ibid.*, **98**, 1986 (1976).
12. P. Crabbé and C. Djerassi, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry", Holden-Day, Inc. San Francisco, 1965, p. 16.
13. Compound 4d corresponds to compound 21 of reference 2 for which a molecular ellipiticity [θ] of -132 was recorded; this corresponds to $\alpha = -1.61$. However, quantitative comparison of our results with those of Sundararaman and Djerassi[2] is not possible since different solvents were employed for rotation measurements in the two investigations.
14. IR($CHCl_3$) 1720 cm^{-1}; NMR, δ($CDCl_3$) 2.32 (s, 6H). The corresponding undeuterated bromoketone 6a has previously been obtained (m.p. 76-77°) by the action of hydrobromic acid on nopinone: A. Van der Gren, L. M. van der Linde, J. G. Witteveen, and H. Boelens, *Rec. Trav. Chim.*, **90**, 1034 (1971).
15. J. Hine and W. S. Li, *J. Am. Chem. Soc.*, **97**, 3550 (1975); see also J. Hine, *Accounts of Chemical Research*, **11**, 1 (1978).
16. We are grateful to Professor A. F. Schreiner for the ORD measurements.

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