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ASYMMETRIC TANDEM ADDITIONS TO CHIRAL 2-NAPHTHYLOXAZOLINES. THE SYNTHESIS OF ENANTIOMERICALLY PURE 1,2,2-TRISUBSTITUTED-1,2-DIHYDRONAPHTHALENES

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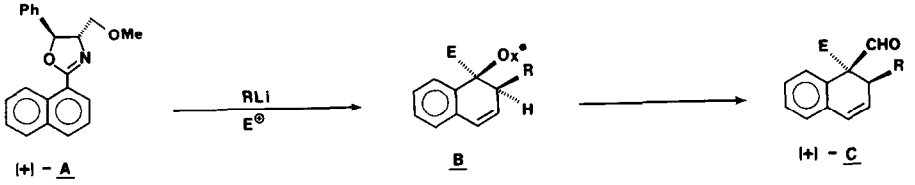
Summary: Addition of organolithium reagents to optically active 2-naphthyloxazolines followed by trapping with methyl iodide gives, after oxazoline removal, the titled compounds whose absolute configuration was determined by x-ray diffraction.

We recently described the efficient addition of organolithium reagents to naphthalene containing the chiral oxazoline, (+)-A followed by electrophilic trapping[1]. The diastereomeric ratios of B (8.5-9.5:1) were found to contain only trans tandem addition products, which were easily purified by chromatography. A three step, efficient process was used to



(+) - A B (+) - C

remove the chiral auxiliary furnishing the enantiomerically pure aldehydes (+)-C. Thus, two chiral elements were introduced into the naphthalene ring in a single step (A→B). It soon became apparent that for some projected natural product syntheses, this tandem alkylation had to show similar stereoselectivity in the 2-naphthyl system 1. The possibility also arose that regiochemical selectivity (to either adjacent 1- or 3-positions) may also pose problems for this route to substituted dihydronaphthalenes[2]. We now describe our results with the 2-naphthyloxazoline, (+)-1, which demonstrate that the tandem additions proceed with both a high degree of stereo- and regioselectivity (Table).

Addition of organolithium reagents to (+)-1, under conditions depicted in the Table, followed by trapping of the intermediate lithioazaenolate with methyl iodide[3] gave the

dialkylated dihydronaphthalene 2 in good yields with generally high diastereoselectivity. The process is also devoid of any cis-addition products, 2a, with the only impurity being that derived from diastereofacial entry of the organolithium. Thus, entry of RLi from the bottom (re-face) of the naphthalene ring generates the major isomer, while the minor isomer results from RLi entry from the topside (si-face). Confirmation of the absolute stereochemistry of the major product (2) was obtained by a single crystal x-ray study on 2 (R=Ph, mp 133-134°). The ORTEP structure (Fig. 1) clearly shows the 1S, 2S configuration for the phenyl and methyl respectively[4]. Thus, the same sense of asymmetric addition to the naphthalene occurs in the 2-naphthalene system, as was observed for the 1-naphthalenes[1]. Furthermore no detectable products were found resulting from addition to 1 in the 3-position. Another interesting aspect of the process is the lack of sensitivity to the temperature of the organolithium addition. Thus the ratio of diastereomers in 2 were only slightly changed (Table) whether the addition was carried out at -78° or 25°. Similarly, the ratios were unaffected in the presence of HMPA as a cosolvent.

TABLE Addition to 1 and Cleavage to Enantiomerically Pure Aldehydes 4

					Aldehydes, 4	
RLi	Equiv.	T°,time[a]	% yield[b]	Diast. Ratio[b] 2	% yield[c] (from 2)	$[\alpha]_D CHCl_3$(c)[d]
n-Bu	1.1	-78°, 2h	85	98:2	81	+190.8°(1.0)
n-Bu	1.1	25°, 5 min	70	92:8	--	
n-Bu	1.1	-78°(HMPA),2h	92	98:2	--	
Me	2.0	-30°, 15h	67	91:9	65	-85.8° (0.5)
Ph	2.0	-30°, 5h	89	90:10	89	-333.6°(0.5)
t-Bu	2.0	-100°, 1.5h	74	76:27	70	+244.4°(0.7)

a) Conditions for addition of organolithiums, methyl iodide added in all cases at -78°.

b) Yields are for isolated mixture of diastereomers of 2 and diastereomeric ratios determined by HPLC (Sorbax, 20% THF-Hexane, 1 ml/min). c) The minor diastereomer in 2 was removed by radial chromatography (20% ethyl acetate-hexane, silica gel) prior to oxazoline removal. HPLC and 270 MHz NMR confirmed homogeneity of 2. Yields of homogeneous product.

d) Rotations for pure homogeneous product.

The minor diastereomer in 2 was readily removed by chromatography furnishing the diastereomerically pure (HPLC, CMR) materials. Cleavage to the enantiomerically pure aldehydes 4 was performed by two related methods. Originally, the quaternization of the oxazoline nitrogen was accomplished using methyl fluorosulfonate ("magic methyl," 3.5 equiv, CH_2Cl_2, 25°, 15 h) followed by direct addition of $NaBH_4$ (4 equiv in MeOH-THF, 0°) which reduced the iminium linkage to 3 in 5 min (mixture of diastereomers). The mixture was diluted with water, CH_2Cl_2 added, and the layer separated, washed with water, and concentrated. The residue of crude 3 was stirred in THF-water with excess oxalic acid (3h, 25°) affording pure 4 after radial chromatography. After this cleavage was accomplished, the future unavailability

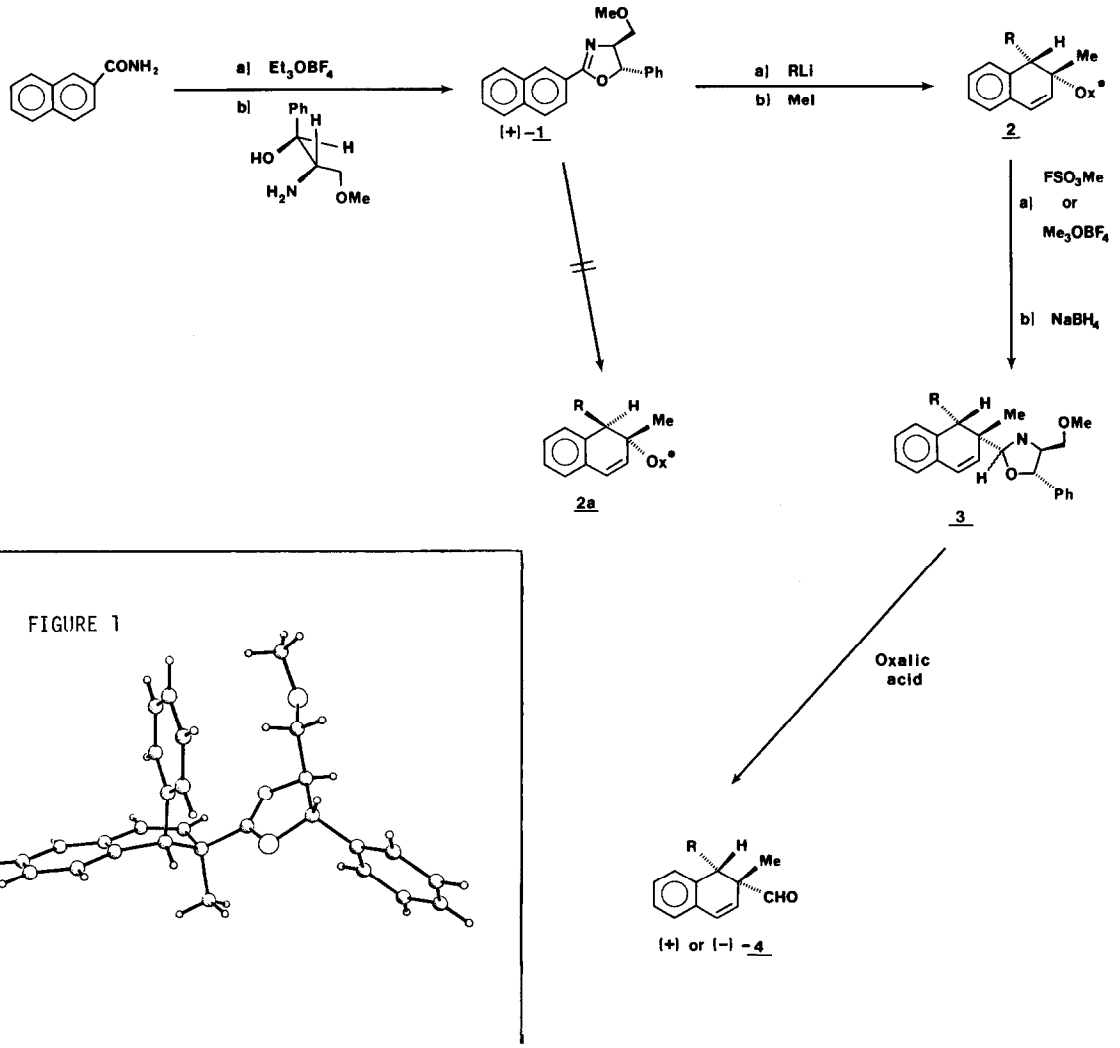


FIGURE 1

of "magic methyl"[5] caused us to develop an alternative method using Me_3OBF_4[6] in its place. It was found that Me_3OBF_4 (2.0 equiv, CH_2Cl_2, 8h) completely quaternizes 2 and reduction with sodium borohydride and hydrolysis (as above) gave comparable yields of the aldehyde, 4.

This facile and efficient route to chiral dihydronaphthalenes now opens the way to a number of naturally occurring and biologically important substances whose synthesis is in progress.

REFERENCES AND NOTES

1. B. A. Barner and A. I. Meyers, J. Am. Chem. Soc. 106, 1865 (1984)
2. Prepared by treating 2-naphthamide with 1.2 equiv Et_3OBF_4 in 1,2-dichloroethane (25°, 24h) then addition of 1.2 equiv S,S-methoxyamino alcohol according to previously described procedure (cf. ref. 1). (+)-1 was obtained in 68% yield, $[\alpha]_D$ 124.3° (c 2.8, $CHCl_3$). Additions to the 3-position would appear unlikely due to the destruction of the aromaticity in both rings of the naphthalene nucleus.
3. In addition to methyl iodide, other electrophiles such as PhSSPh, $ClCO_2Me$, H^+ also provide products with high trans ratios and comparable diastereofacial efficiency.
4. The absolute configuration of the chiral oxazoline 1 has been shown to be 4S, 5S at the methoxymethyl and phenyl group respectively; see: A. I. Meyers, M. A. Hanagan, L. M. Trefonas, R. J. Baker, Tetrahedron 39, 1991 (1983), and earlier references therein.
5. Health restrictions placed on "magic methyl" have caused suppliers to cease sales of this reagent as of October 1983.
6. Alfa; Org. Syn. Coll. Vol. 5, 1096. Attempts to use Et_3OBF_4 failed to give the N-ethyl quaternary salt of 2.

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