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ENANTIOSELECTIVE [2,3] WITTIG RING CONTRACTION INDUCED BY CHIRAL BASES. THE TOTAL SYNTHESIS AND ABSOLUTE CONFIGURATION OF (+)-ARISTOLACTONE

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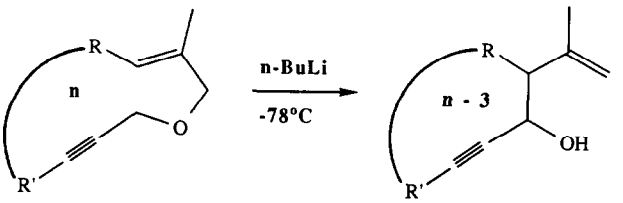
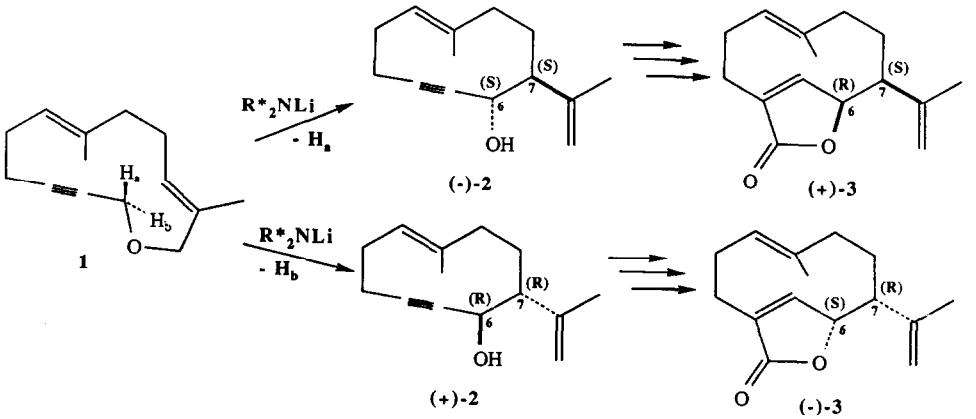
Abstract: [2,3] Wittig ring contraction of the achiral 13-membered acetylenic ether **1** via treatment with lithio (*R,R*) or (*S,S*)-*bis*-(1-phenylethyl)amide afforded the (*R*)-(+) or (*S*)-(-)-propargylic alcohol (+)-**2** or (-)-**2**, respectively, of >60% ee in 75% yield.

We recently described a new route to medium and large ring carbocyclic compounds via Wittig ring contraction of macrocyclic propargylic allylic ethers.[1,2]

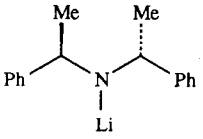


The rearrangement was found to occur readily under mild conditions with good to excellent diastereocontrol. However, a major drawback of this approach to natural product synthesis stems from the absence of chiral control elements and the resultant production of racemic rearrangement products. As a possible solution to this problem, we considered the use of chiral bases to initiate enantioselective rearrangements. The 13-membered ether **1**, recently prepared in connection with our total synthesis of (±)-aristolactone,[2,3] seemed particularly attractive by virtue of its rigidity and the conformationally enforced proximity of the reacting centers. Accordingly, we hoped to differentiate between the enantiotopic propargylic methylene protons H_a and H_b. Implicit in a successful application is the requirement that the intermediate carbanion retain its sense of chirality either as a consequence of constraints in the macrocyclic system or early C-C bond formation in the ensuing [2,3] rearrangement.

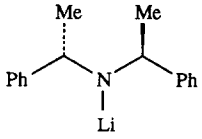


To test the feasibility of the foregoing concept we selected lithio (*R,R*) and (*S,S*)-*bis*-(1-phenylethyl)amide (*R,R*-**4** and *S,S*-**4**) as the chiral bases. These are readily prepared via hydrogenation of the

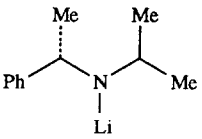
imines derived from (*R*) or (*S*)-1-phenylethylamine and acetophenone.[4] The (*S,S*) base was used by Whitesell[5] in his studies on enantiodirected epoxide eliminations and more recently by Hogeveen for the enantioselective deprotonation of racemic 2,2,6-trimethylcyclohexanone.[6] To date there have been no reported efforts to induce enantioselectivity in [2,3] Wittig rearrangements with a chiral base.



(R,R)-4



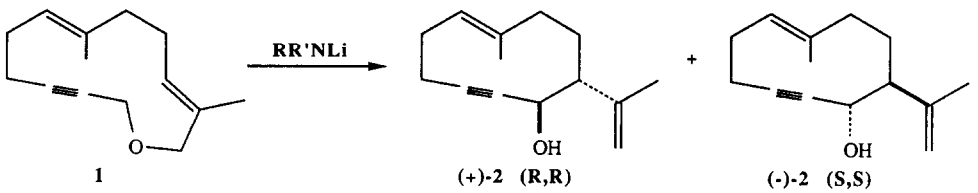
(S,S)-4



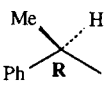
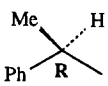
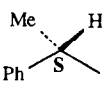
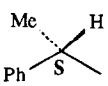
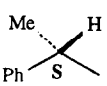
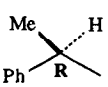
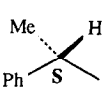
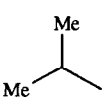
(S)-5

Ether **1** was prepared from geranyl acetate as previously reported.[2] Treatment with the base *R,R*-**4** in THF at -20°C afforded the optically active alcohol (+)-**2** of *ca.* 60% enantiomeric excess in 75% yield.[7] Under comparable conditions the base *S,S*-**4** gave rise to the enantiomeric alcohol (-)-**2** of *ca.* 65% ee.[7] The use of ether or THF-pentane as solvent led to rearranged product of considerably lower ee (Table 1).

Table 1. Enantioselective [2,3] Wittig Ring Contraction



1 (+)-2 (R,R) (-)-2 (S,S)

R	R'	Solvent	T (°C)	t (min)	Yield	$[\alpha]_D$	ee[7]
		THF	-35 to -25	60	78%	+33.4°	73%[a]
"	"	THF	-20	40	75%	+28.5°	62%[a] 57%[b]
		THF	-70 to -15	45	82%	-32.9°	71%[a] 64%[b]
"	"	Et_2O	-25 to -15	30	70%	+4.2°	9%[a]
"	"	THF-pentane (1:9)	-25 to 0	90	68%	-20.6°	45%[a]
		THF	-70 to 0	120	86%	0	0
		THF	-20	60	82%	+0.9°	2%[a]

[a] from optical rotation

[b] from Mosher ester

As expected, the meso base *R,S*-4 afforded racemic product. Interestingly, the chiral (*S*)-1-phenylethyl-isopropyl amide base (5) afforded alcohol 2 of negligible ee.

The configuration of the rearranged alcohols (+)-2 and (-)-2 was tentatively assigned from comparative chemical shift data on the (*S*)-O-methyl mandelic esters 6 and 7.[8] These esters were readily separated by column chromatography on silica gel. The C-7 allylic proton of ester 6 derived from the (+)-alcohol appeared at higher field (2.46 ppm) than the equivalent proton (2.60 ppm) in ester 7 derived from the (-)-alcohol. Accordingly (Fig. 1), the (+)-alcohol must possess the (*R*) and the (-)-alcohol the (*S*) configuration.[8]

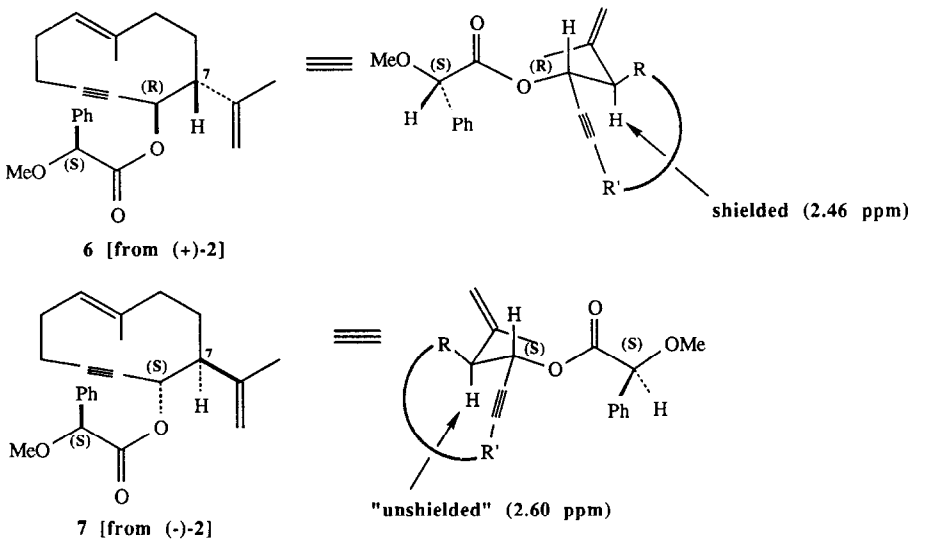
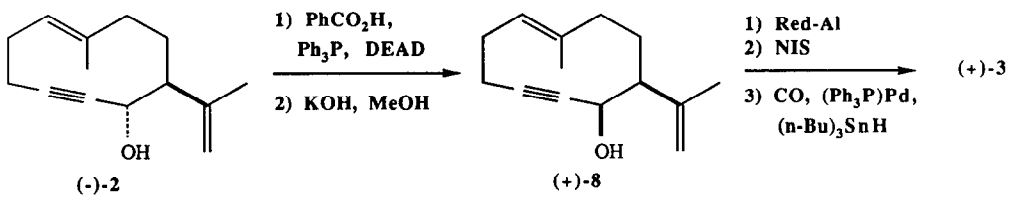


Figure 1. Assignment of absolute configuration to alcohols (+)-2 and (-)-2 from ^{1}H NMR chemical shifts of (*S*)-O-methyl mandelates 6 and 7.

As a further check on the enantioselectivity of the rearrangement we converted the (*S*)-alcohol (-)-2 of *ca.* 70%[9] ee to natural aristolactone (+)-3 by the previously reported sequence.[2]



The measured rotation of our synthetic product ($[\alpha]_D$ +85.4°) compared favorably with the reported rotation ($[\alpha]_D$ +156°) for the natural product considering the ee of the starting alcohol (-)-2.[10] This synthesis constitutes the first proof of absolute configuration for aristolactone and demonstrates for the first time the use of a chiral base to induce enantioselective [2,3] Wittig rearrangement.

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References and Notes

1. Marshall, J. A.; Jenson, T. M.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 4316.

2. Marshall, J. A.; Lebreton, J.; DeHoff, B. S.; Jenson, T. M. *Tetrahedron Lett.* **1987**, *28*, 723. For a related approach see Takehashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. *J. Org. Chem.* **1986**, *51*, 4315.

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7. Separation of the diasteromeric (*S*)-O-methyl mandelates by column chromatography followed by cleavage of each with MeOH, KOH at 25°C led to (+)-**2**, $[\alpha]_D$ +46.1 ($CHCl_3$, c 3.80) and (-)-**2**, $[\alpha]_D$ -45.7 ($CHCl_3$, c 3.71). Values for optical purities of **2** obtained from Mosher ester analysis were somewhat lower than those calculated from optical rotation data. The origin of this discrepancy has not yet been determined.

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