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PREPARATION OF (-)-ARISTOLOCHENE FROM (+)-VALENCENE: ABSOLUTE CONFIGURATION OF (+)-ARISTOLOCHENE FROM *ASPERGILLUS TERREUS.*

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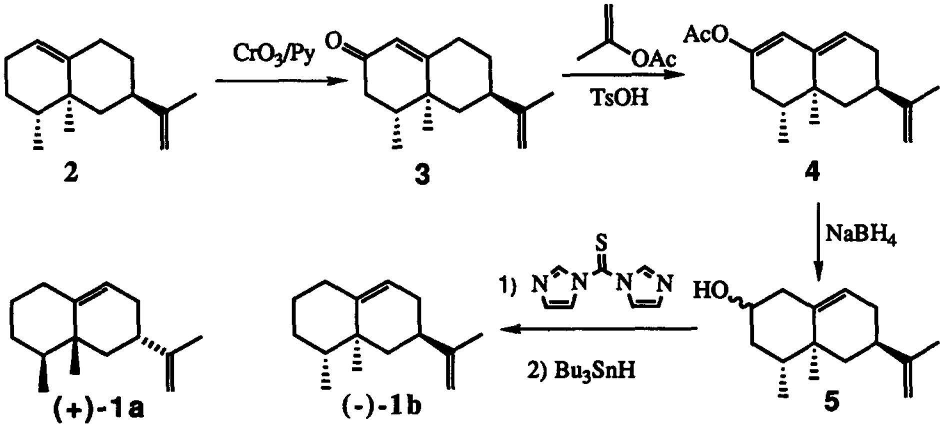
Summary: The absolute configuration of (+)-aristolochene (**1a**), isolated from *Aspergillus terreus*, has been established by direct comparison with a sample of (-)-aristolochene (**1b**) prepared from (+)-valencene (**2**).

We recently reported the isolation and structure elucidation of the sesquiterpene hydrocarbon aristolochene (**1a**) from mycelial extracts of the fungus *Aspergillus terreus*.[1] We have also found that a cell-free extract of *A. terreus* will catalyze the cyclization of farnesyl pyrophosphate to aristolochene and have reported experiments bearing on the mechanism and stereochemistry of this transformation.[2] In connection with this work, it became essential to know the absolute configuration of the fungal aristolochene. The (-)-enantiomer of aristolochene (**1b**) was first isolated in 1973 from the plant, *Aristolochia indica* and assigned the illustrated (4*R*, 5*S*, 7*R*) configuration based on conversion to a reduction product of (+)-valencene.[3] Unfortunately, the small (1-2 mg) quantities at hand of the relatively volatile fungal metabolite and the unavailability of the plant material made risky the assignment of the configuration of **1a** based exclusively on comparison with literature optical rotations. In this report, we describe the unambiguous establishment of the absolute configuration of the *A. terreus* aristolochene by comparison of its chiroptical properties with that of semisynthetic (-)-aristolochene (**1b**), synthesized from naturally occurring (+)-valencene (**2**)[4] in 5 steps, as shown in Scheme 1.[5]



Scheme 1

Allylic oxidation of (+)-valencene (**2**) with CrO_3/Py in methylene chloride as previously described[6] gave nootkatone (**3**). The enone was deconjugated by reduction of the derived dienol acetate (**4**)[7] with $NaBH_4$.[8] The resulting mixture of epimeric alcohols (**5**)[7,9] (75 % from **3**) was reduced to the corresponding hydrocarbon in 65 % yield by sequential treatment with thiocarbonylimidazole and Bu_3SnH in benzene.[10] The resulting (-)-aristolochene (**1b**) was identical by high-field ^{1}H and ^{13}C NMR and capillary gas chromatographic retention time to aristolochene isolated from *A. terreus*. For circular dichroic studies, **1b** was purified using SiO_2 impregnated with 15 % silver nitrate. Authentic (+)-aristolochene (**1a**), isolated from mycelial extracts of *A. terreus* as previously described,[1] was purified in like manner. The CD spectra and optical rotation ($[\alpha]_D$) of each aristolochene sample were recorded, as summarized in Table 1.

Table 1. Comparison of (+)- and (-)-Aristolochene

	(+)-aristolochene[a]	(-)-aristolochene[b]
Molar C D $\Delta\varepsilon$	-0.311 L/mol•cm	+0.282 L/mol•cm
λ_{max}	202.2 nm	200.2 nm
Optical rotation, $[\alpha]_D$	+79.4° (c=0.01763, hexane)	-75.64° (c=0.078, hexane)[c]

a) Isolated from *A. terreus*. b) Synthesized from (+)-valencene. c) $[\alpha]_D$ (lit[3]) -76.47°.

From the above data, it is clear that the fungal sesquiterpene (+)-aristolochene, isolated from *A. terreus*, has the absolute configuration represented by **1a**. Although no oxidized metabolites with the aristolochene skeleton have been isolated from *A. terrreus*, the fungal metabolites sporogen AO-1 (*ex A. oryzae*)[11a] and PR toxin (*ex P. roqueforti*) as well as the related eremofortins[11b] all belong to the same absolute configurational series as **1a**.

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