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Enantioselective synthesis of the volatile anesthetic desflurane

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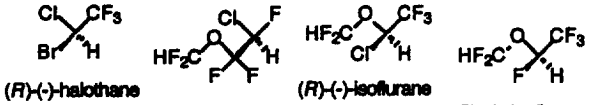
Abstract: The first enantioselective synthesis of the commercial volatile anesthetic desflurane is reported. Treatment of (*R*)-(−)-isoflurane with BrF_3 gives (*S*)-(+)-desflurane with >96% inversion of configuration. This constitutes a correction of previously reported results. © 1997 Elsevier Science Ltd

Syntheses of highly pure individual enantiomers of the volatile anesthetics halothane, enflurane, and isoflurane have appeared recently.[1] Preparative chromatographic separations of the enantiomers of enflurane, isoflurane, and desflurane have also been successful.[2] These studies were undertaken with the anticipation that one enantiomer may exhibit a significantly improved pharmacological profile versus the other or the racemate. Thus far, the most promise has been shown by (*S*)-(+)-isoflurane, which has 50% more anesthetic potency than its enantiomer.[3]



As part of a continuing program,[1b,c,4] we wish to report the synthesis of the desflurane enantiomers.[5] Because abundant supplies of the enantiomers of isoflurane were available to us,[1b] it appeared that S_N2-style displacement of chloride by fluoride would be the simplest method (Table 1). First, an accurate method for determination of the ee of the product had to be developed. Taking a cue from an article[6] describing separation of the enantiomers of the other three anesthetics by capillary GC, we found that the stationary phase Lipodex® A (hexakis(2,3,6-tri-*O*-pentyl)-α-cyclodextrin, supplied by Macherey–Nagel, Düren, Germany; ES Industries, NJ, USA) easily resolved the desflurane enantiomers at ambient temperature.

The first conditions tried (entry 1) are those used in the production process of *rac*-desflurane.[7] Even at low conversion of isoflurane, racemic product resulted after distillation of the reaction mixture. The remainder of the product mixture was (*R*)-(−)-isoflurane with an ee of only 67%. These results would seem to indicate an S_N1-type reaction where a planar achiral intermediate is involved. BrF_3 was then tried as the fluoride source, with or without added solvent.[8] The solventless reactions (entries 3 and 4; one equivalent of BrF_3 used) were unpredictable, sometimes requiring an induction period of an hour. Use of $CFCl_2CF_2Cl$ as solvent with two equivalents of BrF_3 resulted in a more controlled reaction, but the yield and ee were both low. Use of the non-polar solvent bromine in conjunction with one equivalent of BrF_3 allowed a smooth, high-yielding conversion of isoflurane with good stereochemical control. The best conditions (entry 5) resulted in >96% inversion of configuration, giving (*S*)-(+)-desflurane with $[\alpha]_D^{25}$=+29.0 (neat). A rough correlation between solvent polarity and ee was noted; as the polarity of the solvent was lowered, the level of stereochemical control increased, indicating a

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Table 1. Synthesis of desflurane from isoflurane

isoflurane desflurane

entry	isoflurane enantiomer [ee]	reagent	solvent	T (°C)	yield	desflurane enantiomer [ee]
1	(*R*)-(-) [99.0%]	HF/SbCl5	HF	-12 to -10	19%	racemic
2	(*R*)-(-) [99.0%]	BrF_3	$CFCl_2CF_2Cl$	0 to rt	30%	(*S*)-(+) [59.2%]
3	(*S*)-(+) [97.0%]	BrF_3	BrF_3	rt	20%	(*R*)-(-) [80.0%]
4	(*R*)-(-) [99.0%]	BrF_3	BrF_3	0	36%	(*S*)-(+) [86.1%]
5	(*R*)-(-) [98.5%]	BrF_3	Br_2	-18 to -10	71%	(*S*)-(+) [91.7%]
6	(*S*)-(+) [>99%]	BrF_3	Br_2	-20 to -15	78%	(*R*)-(-) [91.1%]

shift from an S_N1 to an S_N2 mechanism. A referee has suggested that another function of bromine may be to complex with the chlorine atom and thereby assist it in departure.

In an earlier disclosure,[9] it was reported that this transformation gave the unexpected result of retention of configuration. At the time of that account, it was thought that the absolute configuration of (+)-desflurane was *R*, based on spectroscopic evidence.[10] This anomalous result and subsequent reports of a C–C bond cleavage reaction that resulted in clean inversion of configuration[4a,b] (the absolute configuration of the product was correlated with that of desflurane) spurred a re-evaluation of the original determination of desflurane's absolute configuration. A recent report[11] of the X-ray crystal structure of (+)-desflurane makes it nearly certain that its absolute configuration is *S*, although a measure of doubt remains because of the small crystallographic difference between H and F. Subsequent to this, a correction of the original faulty spectroscopic determination has appeared.[12]

Desflurane is the last of the commercial chiral volatile anesthetics to be prepared in enantiomerically enriched form. Preliminary testing[5] of non-racemic desflurane on rodents has revealed that (*S*)-(+)-desflurane is only slightly more potent in mice than the racemate or the other isomer; in rats, recovery time after administration of the (*R*)-(−)-isomer is about four times as short as when the racemate is used and about three times as short as when the other isomer is used. At this point, these results are significant only in the academic arena, where they could be used in ongoing studies of the molecular mechanism of anesthesia.[3] To our knowledge, an enantiomerically enriched anesthetic has never been administered to a human subject. Now that all the anesthetics are potentially available as essentially single enantiomers in large quantities, this ultimate testing may take place.

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