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Asymmetric Synthesis of the Antiarrhythmia Agent *d*-Sotalol

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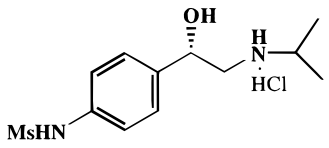
Abstract:

A chiral synthesis of *d*-Sotalol was developed starting from commercially available 4′-(chloroacetyl)methanesulfonanilide (2).

Reentrant ventricular arrhythmia is a major factor for most cases of sudden cardiac death[1] (SCD), which is responsible for 40 000 deaths in the United States annually. Class III antiarrhythmia compounds,[2] such as *d*-Sotalol [**1**, 4′-[2-(isopropylamino)-1-hydroxyethyl]methanesulfonanilide hydrochloride, MJ-1999],[3] Sematilide,[4] Ibutilide,[5] E-4031,[6] and UK-68,798,[7] effectively control such arrhythmia, and these drugs are in various stages in clinical trials. In the past few years, considerable progress was made in the preparation of *d*-Sotalol by chiral chromatographic separation,[8] resolution[3b] of racemic Sotalol with chiral l-mandelic acid, and chiral homogeneous hydrogenation[9] of 4′-[(isopropylamino)acetyl]-methanesulfonanilide hydrochloride.



1, d-Sotalol

This communication describes the enantioselective total synthesis of *d*-Sotalol starting from commercial 4′-(chloroacetyl)methanesulfonanilide (**2**). The key step in the synthesis involves chiral reduction of the carbonyl group in **2** employing the CBS reduction.[10] In addition to reduction of this substrate, a variety of related prochiral and nitrogen-containing aromatic ketones[11] were reduced with borane in the presence of catalytic CBS compound (*S*)-2-methyloxazaborolidine **3** [(*S*)-Me-CBS-OB],[12] and the experimental results are summarized in Table 1. The chiral alcohols[13] were obtained in good to excellent yields with moderate to excellent enantiomeric excesses. Configurations of the chiral alcohols are predicted on the basis of chiral recognition mechanism[10a,h] developed for reduction of ketones by **3**. Encouraged by the results in Table 1, asymmetric reduction of **2** gave the chloro alcohol (**4**) in 87.2% yield and 95% optical purity.

Further optimization of a number of conditions for this reaction were explored to improve the optical purity of **4** and to develop a convenient and scalable process. Factors studied included solvents, mode of addition, amounts of chiral reagent (**3**), and temperature (Table 2). These experiments were performed by adding 1 M BH_3—THF (1.5 mL) to a mixture of **2** (1.825 mmol) and (*S*)-Me-CBS-OB (**3**, 5.9 mol %) in a solvent (4 mL) over 7 min followed by further reaction for 0.5 h. Among various solvents surveyed, diethyl ether and *tert*-butyl methyl ether were the best for this asymmetric reduction.

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(12) (*S*)-Me-CBS-OB was purchased from Lancaster Synthesis Ltd, P.O. Box 1000, Windham, NH 03087. For its preparations, see ref 10c and the following: Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751.

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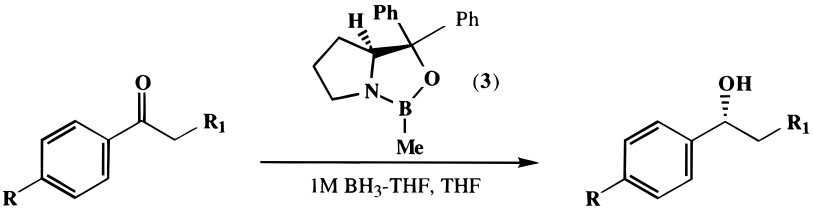
(15) HPLC conditions: column, Apex ODS 5μ (15 cm); mobile phase, 65% CH_3CN and 35% PH 5.7 phosphate buffer; flow rate, 1 mL/min; detection, 225 nm; retention times of the bis Mosher ester of **4** and its enantiomer, 14.6 and 15.7 min.

 S1083-6160(96)00043-6 CCC: $14.00

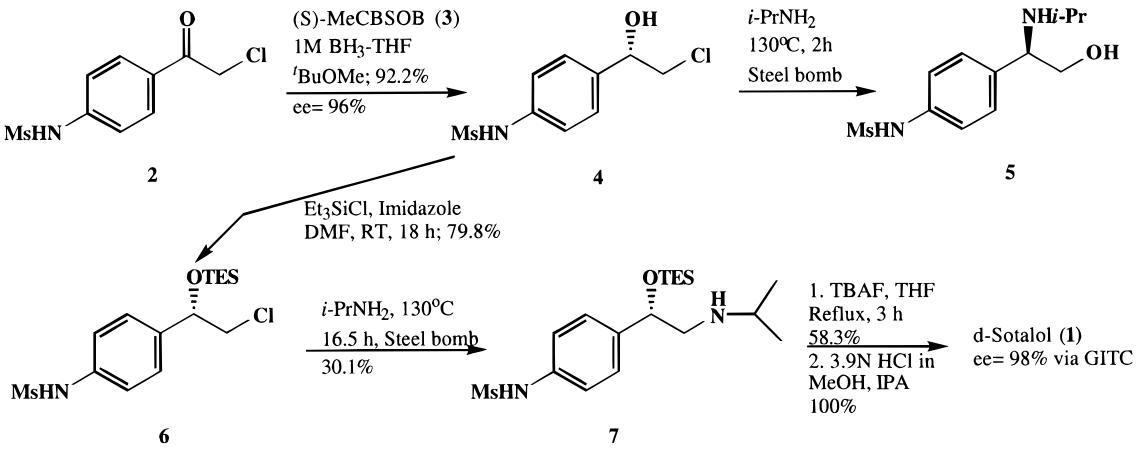
Table 1



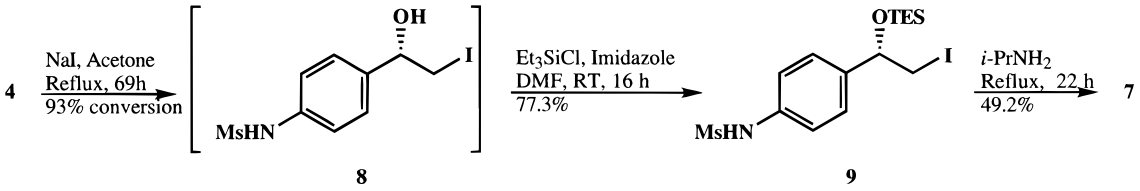
R, R_1[a]	**3** (mol %)	yield (%)	ee[b]	R, R_1[a]	**3** (mol %)	yield (%)	ee[b]
NHMs, H	2.3	81.2	98 (*R*)	F, H	1.6	91.3	88 (*R*)
NMs_2, H	2.5	79.3	100 (*R*)	NBzMs, Cl	2.3	78.4	82 (*S*)
NBzMs, H	2.0	93	85 (*R*)	NBzMs, Cl	5.0	84.8	95 (*S*)
NBnMs, H	2.3	89.4	79 (*R*)	NHMs, Cl (**2**)	5.7	87.2	95 (*S*)
NO_2, H	2.0	84.8	85 (*R*)	F, Cl	1.5	100	90 (*S*)
CN, H	2.2	56.6	33 (*R*)				

[a] Compounds were reduced typically as follows: Solutions of the ketone (1.54 mmol, 1.0 equiv) in anhydrous THF (8 mL) and BH_3−THF (1 M, 0.51 equiv) were simultaneously added over 2 min to the catalyst (**3**) in 1 M BH_3−THF (0.11 equiv) at room temperature and stirred for 0.5−1 h. [b] Enantiomeric excess (ee) was determined after the conversion of the alcohol product into its Mosher ester[14] followed by integration of the benzylic proton.

Scheme 1

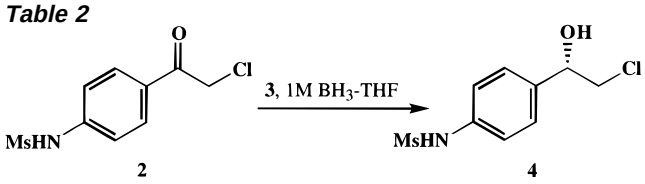


Scheme 2



The complete synthesis of *d*-Sotalol is outlined in Scheme 1. The chiral chloro alcohol (**4**)[16] obtained by enantioselective reduction in *t*-BuOMe was treated with isopropylamine at 130 °C in a steel bomb to give **5**, instead of *d*-Sotalol, which formed presumably from an epoxide intermediate. To circumvent this, **4** was silylated with triethylsilyl chloride (TESCl) in the presence of imidazole in DMF at rt for 18 h to provide **6** in 79.8% yield after silica gel chromatography. Nucleophilic displacement of **6** with isopropylamine (130 °C, steel bomb, 16.5 h) followed by purification furnished the TES-protected *d*-Sotalol (**7**) in 30.1% yield. Desilylation of **7** in THF with 1 M TBAF−THF (reflux, 3 h) afforded *d*-Sotalol as a free base in 58.3% yield, which on being mixed as a slurry in isopropyl alcohol with 3.9 N HCl in MeOH furnished *d*-Sotalol (**1**) in a quantitative yield with an ee[3b] of 98%.

Table 2



entry	solvent	temp	yield (%)	ee[a]
1	THF	0 °C	100	86
2	THF	rt	83.4	89
3	dioxane	rt	93.3	87
4	Et_2O	rt	95.5	97
5	*n*-Bu_2O	rt	b	87
6	*t*-BuOMe	rt	92.2	96

[a] Enantiomeric excess was determined by HPLC analysis[15] of bis Mosher esters. [b] Reaction was incomplete due to the insolubility of **2** and **4** (21:79, by ^{1}H NMR).

(16) It was also prepared in 88% ee from **2** by employing (+)-*β*-chlorodiisopinocampheylborane (THF, rt, 3 days, 65% conversion; 50% yield). For a related reference, see: Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 5446.

In further efforts to scale up the production of TES-protected *d*-Sotalol (**7**), which is critical in our synthetic plan, and to avoid use of a steel bomb, **4** was subjected to the Finkelstein conditions[17] (saturated NaI in acetone, reflux, 69 h) followed by silylation (TESCl, imidazole, DMF, rt, 16 h) (Scheme 2). The crude product obtained after workup was purified by silica gel chromatography to furnish the iodo silyl ether (**9**), containing 7−9% of its chloro analog (**6**), in 77.3% yield. As anticipated, S_N2 displacement of the iodo group in **9** is facile and was carried out in neat isopropylamine at reflux for 22 h to give the TES-protected *d*-Sotalol (**7**) in 49.2% yield after silica gel chromatography.

In conclusion, a simple and new asymmetric synthesis of *d*-Sotalol has been accomplished from **2**. It was discovered that **2**, even though it contains an acidic methanesulfonamide proton, reacted rapidly with borane in the presence of (*S*)-Me-CBS-OB (**3**) to provide the chiral chloro alcohol (**4**) with excellent optical purity.

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[⊗] Abstract published in *Advance ACS Abstracts,* February 15, 1997.