Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: Patrick Smith , Paul R. Brodfuehrer , John L. Dillon & Purushotham Vemishetti (1995): A Short Synthesis of d-Sotalol, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:7, 1093-1098

To link to this article: http://dx.doi.org/10.1080/00397919508012672

SYNTHETIC COMMUNICATIONS, 25(7), 1093-1098 (1995)

A SHORT SYNTHESIS OF d-SOTALOL

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ABSTRACT: Asymmetric synthesis of d-Sotalol (2) was accomplished by chiral homogenous hydrogenation of (4-isopropylaminoacetyl)methanesulfonanilide hydrochloride (1).

Clinical candidate d-Sotalol (2) is a unique molecule which has an acidic methanesulfonanilide moiety and has exhibited an interesting class-III electrophysiological property[1,2] that is effective against ventricular arrhythmias. It was prepared in our laboratory by employing the asymmetric CBS reduction of (4-chloroacetyl)methanesulfonanilide followed by subsequent chemical manipulations.[3] This technology, however, does not provide practical and economical access to 2 due to the modest overall yield, multiple process steps and the use of an expensive chiral reagent. As part of our ongoing program, we wish to report an efficient and short synthesis of d-sotalol using chiral

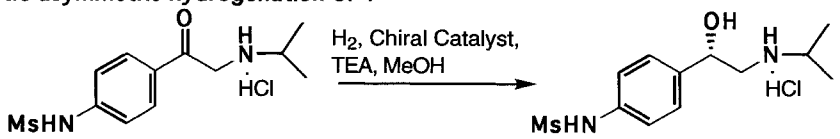
homogenous hydrogenation of (4-isopropylaminoacetyl)methanesulfonanilide hydrochloride (**1**).[4]

Chiral C_2-axis bidentate phosphines are the chiral auxiliaries of choice in combination with Rh/Ru metal for a number of asymmetric reactions[5], such as hydrogenation, hydrosilylation, hydroboration, isomerization, and C-C bond formation. For the past decade, Noyori[6] and Achiwa[7] have made significant contributions in the field of asymmetric hydrogenation of prochiral ketones and its α-substituted ones. Another added advantage of this chiral homogenous hydrogenation is that the reagent is needed only in 10^{-2} to 10^{-5} mol %.

A variety of commercially available chiral phosphine reagents,[8] *i.e.*, Rh[(3R,4R-BBDPP)](COD)BF_4 (Deguphos), $RhClO_4$[bicyclo(2.2.1)hepta-2,5-diene][(S,S)-Chirapohos] and *in situ* prepared $RhCl_2$[(S,S)-DIOP], $RhCl_2$[(R)-Prophos], $RuCl_2$[(S,S)-Chirapohos] were initially evaluated for hydrogenation (1000 PSI) of **1** in methanol in the presence of triethylamine with various conditions. All of these reactions provided unwanted l-Sotalol in a *disappointing enantiomeric excess*, 0-9.3%, except $RhClO_4$[bicyclo(2.2.1)-hepta-2,5-diene][(S,S)-Chirapohos], which furnished d-Sotalol (**2**) in 34.3% ee.

Next, our attention was directed towards chiral BINAP[8,9], which had been successfully used in homogenous chiral hydrogenations.[6] Results of our study in this regard are depicted in the table, and a quantitative yield of the product was obtained in all cases. It was found that Rh with (R)-BINAP or Ru with (S)-BINAP complexes furnished the desired d-Sotalol. Both reagents, made *in situ*,[11] gave better optical purity compared to the pre-formed ones (Entry 2 *vs*

Table: Catalytic asymmetric hydrogenation of 1



1 2, d-Sotalol

Entry	Reagents	*In situ* formation of Chiral Catalyst	S/C[a]	Conditions	ee (Conf) of 2[b]
1	$(RuCl_2COD)_n$, (S)-BIN AP, TEA		116	1000 PSI, RT, 26.5 h	29.5 (S)
2	$RuCl_2$[(S)-BINAP].TEA[c]		204	1000 PSI, RT, 94 h	39.8 (S)
3	$(RuCl_2COD)_n$, (S)-BINAP, TEA	100°C, 2 h	109	1000 PSI, 50°C, 16 h	52.7 (S)
4	$RhClO_4$[(R)-BINAP].THF[d], TEA		388	1000 PSI, 80°C, 19 h	66.6 (S)
5	"		776	1000 PSI, 80°C, 19 h	45.6 (S)
6[e]	$(RhCl_2COD)_n$, (R)-BINAP, TEA	100°C, 2 h	136	1000 PSI, 80°C, 16 h	78.2 (S)
7	"	100°C, 1.5 h	1083	1000 PSI, 80°C, 16 h	73.6 (S)
8	"	100°C, 1.5 h	148	1000 PSI, 50°C, 16 h	77.0 (S)
9	"	100°C, 3.25 h	179	500 PSI, 50°C, 65.5 h	83.8 (S)
10	"	**100°C, 3.25 h**	**181**	**1000 PSI, RT, 65 h**	**85.0(S)**
11	"	100°C, 3.25 h	1083	1000 PSI, RT, 16 h 1000 PSI, 80°C, 4 h	81.0 (S)

Notes: (a). Substrate to Catalyst; (b). Enantiomeric excess was determined after HPLC analysis of its GITC derivative.[2] (c). The catalyst was prepared according to a literature procedure.[10] (d). Purchased from Aldrich Chemical Co., Milwaukee, US. (e). In this experiment, the hydrogenation of ***1*** *proceeded to 84.5% Conversion.*

3 and Entry 4 & 5 *vs* 6-11). This technique eliminated the handling of air sensitive Rh/Ru-BINAP complex. Interestingly, the use of the $RhCl_2$[(R)-BINAP] catalyst provided a significantly higher enatiomeric excess than that of the $RuCl_2$[(R)-BINAP] reagent. The best enantiomeric excess, 85%, of d-Sotalol (**2**) was obtained from **1** with $RhCl_2$[(R)-BINAP] according to the conditions described in Entry 10 of the table.

Experimental Section

d-Sotalol (2). (4-Isopropylaminoacetyl)methanesulfonanilide hydrochloride (**1**, 500 mg, 1.63 mmol), $(RhCl_2COD)_n$ (4.2 mg, 0.009 mmol), (R)-BINAP (10.2 mg, 0.016 mmol) and anhydrous TEA (27.5 ul, 0.133 mmol) were added to methanol (10 ml) in a steel bomb under an argon atmosphere. After stirring the resulting solution at 100°C for 3.25 h, the reactor was cooled to room temperature and purged with hydrogen three times. It was then pressurized to 1000 PSI with hydrogen and stirred at room temperature for 65 h. The reaction mixture was filtered and evaporated to give a reddish-orange oil which was slurried in 2-propanol to induce crystallization. d-Sotalol (2, ee 85%) was collected by filtration in quantitative yield. Optical purity of d-Sotalol (**2**) was determined according to a literature procedure after making its GITC derivative with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate followed by HPLC analysis.[2]

References

1. Taggart, P., Sutton, P. and Donaldson, R., *Clin. Sci.* **1985**, *69*, 631.

2. Simon, A. and Thomis, J.A., U.S. **1992**, 5,089,526.

3. Brodfuehrer, P.R., Smith, P., Dillon, J.L. and Vemishetti, P., *Communicated to Bioorg. & Med. Chem. Letters.*

4. Uloth, R.H., Kirk, J.R., Gould, W.A. and Larsen, A.A., *J. Med. Chem.* **1966**, 9, 88.

5. Brunner, H., *Synthesis* **1988**, 645; Noyori, R., *Chem. Soc. Rev.* **1989**, *18*, 187; Ojima, I., Clos, N. and Bastos, C., *Tetrahedron* **1989**, 45, 6901; Blystone, S.L., *Chem. Rev.* **1989**, *89*, 1663; Inoguchi, K., Sakuraba, S. and Achiwa, K., *SYNLETT* **1992**, 169; Zassinovich, G., Mestroni, G. and Gladiali, S., *Chem. Rev.* **1992**, *92*, 1051;

6. Noyori, R., Ohkuma, T., Kitamura, S., Takaya, H., Sayo, N.; Kumobayashi, H. and Akutagawa, S., *J. Am. Chem. Soc.* **1987**, *109*, 5856; Kitamura, M., Ohkuma, T., Inoue, S., Sayo, N., Kumobayashi, H., Akutagawa, S., Ohta, T., Takaya, H. and Noyori, R., *J. Am. Chem. Soc.* **1988**, *110*, 629; Noyori, R. and Takaya, H., *Acc. Chem. Res.* **1990**, *23*, 345.

7. Takeda, H., Tachinami, T., Aburatani, M., Takahashi H., Morimoto, T. and Achiwa, K., *Tetrahedron Lett.* **1989**, *30*, 363; Takeda, H., Tachinami, T., Aburatani, M., Takahashi H., Morimoto, T. and Achiwa, K., *Tetrahedron Lett.* **1989**, *30*, 367; Takahashi, H., Sakuraba, S., Takeda, H. and Achiwa, K., *J. Am. Chem. Soc.* **1990**, *112*, 5876; Sakuraba, S., Nakajima, N. and Achiwa, K., *SYNLETT* **1992**, 829.

8. Chiral auxiliaries/complexes were purchased from commercial sources. (3R, 4R)-BBDPP:1-Benzyl-(3R,4R)-bis(diphenylphosphino)pyrrolidine; (S,S)-Chiraphos:(2S,3S)-Bis(diphenylphosphino)butane; (S,S)-DIOP:4S,5S-Bis(diphenylphosphino)methyl-2,2-dimethyl-1,3-dioxolane; (R)-Prophaphos: (1,2R)-Bis(diphenylphosphino)propane; (S/R)-BINAP: (S/R)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl.

9. Takaya, H., Mashima, K., Koyana, K., Yagi, M., Kumobayashi, H., Taketomi, T., Akutagawa, S. and Noyori, R., *J. Org. Chem.* **1986**, *51*, 629.

10. Rychnovsky, S., Griesgraber, G., Zeller, S., and Skalitzky, D.J., *J. Org. Chem.* **1988**, *27*, 566

11. Kitamura, M., Tokunaga, M., Ohkuma, T. and Noyori R., *Tetrahedron Lett.* **1991**, *32*, 4163; Taber, D.F. and Silverberg, L.J., *Tetrahedron Lett.* **1991**, *32*, 4227.

(Received in the USA 15 September 1994)