Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 3226–3229

Asymmetric synthesis of Sulindac esters by enantioselective sulfoxidation in the presence of chiral titanium complexes

Francesco Naso,[a,b] Cosimo Cardellicchio,[a,*] Francesco Affortunato[b] and Maria Annunziata M. Capozzi[c]

[a]*Consiglio Nazionale delle Ricerche, Istituto di Chimica dei Composti Organometallici (ICCOM), c/o Dipartimento di Chimica, Università di Bari, via Orabona 4, 70126 Bari, Italy*
[b]*Dipartimento di Chimica, Università di Bari, via Orabona 4, 70126 Bari, Italy*
[c]*Dipartimento di Scienze Agro-Ambientali, Chimica e Difesa Vegetale, Università di Foggia, via Napoli 25, 71100 Foggia, Italy*

Received 5 October 2006; accepted 13 December 2006

Abstract—High ee values (up to 94–96% ee) and moderate isolated yields (48–50%) were achieved in the preparation of Sulindac alkyl esters. These molecules are simple and straightforward precursors of Sulindac, an anti-inflammatory drug that has also been recently investigated in anti-cancer therapy. The key step of the overall procedure was the enantioselective hydroperoxide oxidation of the Sulindac sulfide alkyl esters in the presence of chiral complexes of titanium with either (*S*,*S*)- or (*R*,*R*)-hydrobenzoin. Various reaction conditions were investigated in order to obtain the best balance between yield and enantioselectivity.

1. Introduction

Sulindac[1,2] {(*Z*)-5-fluoro-2-methyl-1-[*p*-(methylsulfinylbenzylidene]indene-3-acetic acid)} is a well-known non-steroidal anti-inflammatory drug. Recently, different research lines have focussed on the application of Sulindac and its derivatives in cancer research. Attention was devoted to the action of these molecules on the enhancement of cytotoxicity of anti-cancer drugs,[3] the induction of apoptosis on tumour cell lines[4,5] and inhibition of the proliferation of colorectal carcinoma cells.[6] Obviously, investigations on the biological activity of Sulindac and its metabolites require both enantiomers of this molecule. However, only a few successful works have been reported on this topic, the crucial step being represented by an enantioselective metal-[7,8] or bio-catalysed[9,10] oxidation of sulfides.

The asymmetric oxidation of sulfides in the presence of metal complexes is an established and straightforward procedure[11] that was also applied to biologically active molecules.[12] In the case of Sulindac, oxidation of the corresponding sulfide with cumene hydroperoxide (CHP) in the presence of a complex between titanium and diethyl tartrate was unsuccessful.[7] The difficulties were partially overcome by oxidising a smaller, less substituted indenic sulfide intermediate with the above procedure (54–56% yield, 88–90% ee).[7] This intermediate was then transformed into Sulindac by reacting it with glyoxylic acid (28–30% yield).[7] Important progress was made by Bolm et al., who applied an iron catalysed methodology to the oxidation of the same indenic sulfide intermediate (69–71% yield).[8] The procedure that permitted the synthesis of both enantiomers of Sulindac in up to 92% ee has the advantages of using an environmentally friendly metal and mild reaction conditions.

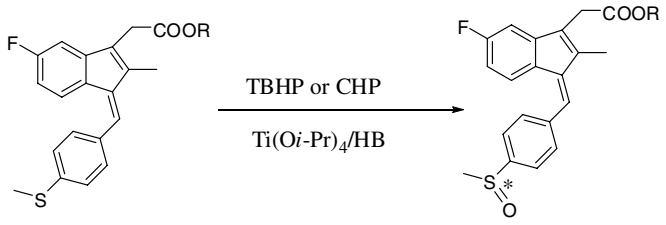
2. Results and discussion

Due to our interest in enantioselective routes to sulfoxides,[13] we chose a different approach to the synthesis of Sulindac, with the aim of avoiding the low yield reaction with glyoxylic acid. Sulindac alkyl esters were considered as convenient precursors, since they can be easily converted into the target molecule by an almost quantitative hydrolysis.[1] Herein, we report the asymmetric synthesis of these compounds by an enantioselective oxidation of the corresponding sulfides with hydroperoxides (Table 1), in the

* Corresponding author. Tel.: +39 0805442077; fax: +39 0805442924; e-mail: cardellicchio@ba.iccom.cnr.it

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.12.002

Table 1. Enantioselective oxidation of Sulindac sulfides alkyl esters with hydroperoxides in the presence of a titanium/hydrobenzoin complex



1a, 1b **2a, 2b**

1a, 2a R = Me. **1b, 2b** R = *tert*-Bu
HB = (*S,S*) or (*R,R*)-hydrobenzoin

Entry	Substrate	Oxidant	Ligand	Temperature	Water[a]	*t* (h)	Solvent	Product	Yield (%)	ee[b] (%)
1	**1a**	TBHP	(*S,S*)	rt	0	42	*n*-Hexane	(*R*)-**2a**	29[c] (31)[d]	88
2	**1a**	TBHP	(*S,S*)	rt	0	44	Toluene	(*R*)-**2a**	47[c] (33)[d]	88
3	**1a**	TBHP	(*S,S*)	rt	0	4	Toluene	(*R*)-**2a**	(40:47:13)[e]	76
4	**1a**	TBHP	(*S,S*)	rt	0.5	48	Toluene	(*R*)-**2a**	49[c]	88
5	**1a**	TBHP	(*S,S*)	rt	0	44	CH_2Cl_2	(*R*)-**2a**	59[f]	52
6	**1a**	TBHP	(*S,S*)	rt	0	46	CCl_4	(*R*)-**2b**	49[c] (38)[d]	96
7	**1a**	TBHP	(*S,S*)	rt	0	4	CCl_4	(*R*)-**2a**	(34:52:14)[e]	77
8	**1a**	TBHP	(*S,S*)	0°	0	48	CCl_4	(*R*)-**2a**	64[c]	71
9	**1a**	CHP	(*S,S*)	rt	0	46	Toluene	(*R*)-**2a**	20[c] (50)[d]	53
10	**1a**	CHP	(*S,S*)	rt	0	28	CCl_4	(*R*)-**2a**	28[f]	32
11	**1a**	TBHP	(*R,R*)	rt	0	43	CCl_4	(*S*)-**2a**	50[c]	94
12	**1b**	TBHP	(*S,S*)	rt	0	47	Toluene	(*R*)-**2b**	49[c]	94
13	**1b**	TBHP	(*S,S*)	rt	0	46	CCl_4	(*R*)-**2b**	48[c]	95
14	**1b**	TBHP	(*S,S*)	rt	0	6	CCl_4	(*R*)-**2b**	54[c]	76
15	**1b**	TBHP	(*R,R*)	rt	0	46	CCl_4	(*S*)-**2b**	49[c]	96

[a] Water/sulfide ratio.
[b] Determined by HPLC [(*R,R*)-Whelk O1 column, eluent *n*-hexane/*i*-propanol/methylene chloride 6:3:1), or NMR [upon addition of (*R*)-3,5-dinitro-*N*-(1-phenylethyl)benzamide].
[c] Isolated yields of the sulfoxide.
[d] Isolated yield of the corresponding sulfone.
[e] Ratios between **1a**:**2a**:**3a** (yields not determined).
[f] Chromatographic yield.

presence of a complex between titanium and (*S,S*)-hydrobenzoin (HB). This oxidation system had been applied by us to prepare (*R*)-benzyl *p*-bromophenyl sulfoxide (85% yield, >98% ee) that represents a general precursor of dialkyl sulfoxides,[14] and aryl β-ketosulfoxides (70–94% yield, 92–>98% ee).[15] Another group has adopted the same methodology in the preparation of an anti-HIV-1 agent.[16] Herein, we oxidise Sulindac sulfide methyl ester **1a**[1,17] to yield sulfoxide **2a**[1,2,18] (Table 1) by adding 1.3 equiv of *tert*-butyl hydroperoxide (TBHP) to 1 equiv of sulfide **1a**, in the presence of 0.1 equiv of a 1:2 complex between titanium(IV) *i*-propoxide and (*S,S*)-hydrobenzoin, according to our procedure.[14,15] The products in the crude reaction mixture were separated by column chromatography on silica gel (eluent ethyl acetate/petroleum ether 1:1).

When the oxidation was performed in *n*-hexane, the sulfide reacted sluggishly (Table 1, entry 1). After 42 h, sulfoxide (+)-**2a** was produced with a high ee value (88% ee), but in low isolated yield (29%). Almost 40% of the starting sulfide **1a** was still present. Furthermore, at variance with other previous cases,[14,15] we observed large amounts of the corresponding sulfone **3a** (31% isolated yield). Therefore, we decided to change the solvent and to perform the same oxidation in toluene at room temperature (Table 1, entry 2). After 44 h, only 6% of the starting substrate **1a** was still present and sulfoxide (+)-**2a** was obtained with 47% isolated yield and with 88% ee, together with the corresponding sulfone **3a** (33% isolated yield). In order to shed light on the mechanism of the formation of sulfoxide **2a**, the same reaction was stopped after 4 h (Table 1, entry 3). The ratios between compounds **1a**:**2a**:**3a** were 40:47:13, sulfoxide **2a** having a 76% ee value. The presence of large amounts of sulfone (Table 1, entry 2) and the observation that the ee value increased over time were indications that the asymmetric synthesis of sulfoxide **2a** followed a two-step mechanism; the first step being the enantioselective oxidation of sulfide **1a**, and the second one a further enantiomeric enrichment of sulfoxide **2a**, due to a kinetic resolution in the process leading to sulfone **3a**. A couple of reactions in which a kinetic resolution step increases the ee of the produced sulfoxides were recently investigated for different sulfides and catalysts.[19–21]

At this stage, the role of water in the reaction was investigated, since its presence is sometimes reported to be crucial in titanium catalysed oxidations.[11] The reaction of entry 2 was repeated by adding 0.5 equiv of water (with respect to the sulfide) during the formation of the titanium catalyst (Table 1, entry 4). Since the result was similar to those of

entry 2, the other reactions were performed without adding water.

After these experiments, we chose to test chlorinated solvents in the oxidation. Methylene chloride was found to be unsuitable since a decrease in the ee value (52%) of sulfoxide **2a** was observed (Table 1, entry 5), as occurred in a previous work.[14] Better results were obtained when carbon tetrachloride was used. After 46 h, sulfoxide (+)-**2a** was obtained (49% yield, 96% ee) together with sulfone **3a** (38%) (Table 1, entry 6). Only small amounts of sulfide **1a** were recovered (7%). The observation of the composition of the same reaction mixture after only 4 h showed that compounds **1a**:**2a**:**3a** were in 34:52:14 ratios and sulfoxide **2a** had 77% ee (Table 1, entry 7). From these results, the mechanistic considerations concerning entry 2 could also be extended to this reaction, that is, a combined mechanism (enantioselective oxidation of sulfide **1a**, followed by a kinetic resolution of sulfoxide **2a**) was acting. The oxidation was then repeated under the same reaction conditions, but at 0 °C for 48 h (Table 1, entry 8). Sulfoxide **2a** was formed (64% yield, 71% ee), together with low amounts of sulfone **3a** (<5%). This experiment was considered of special mechanistic interest, because it showed that it was possible to inhibit the kinetic resolution process, even at longer reaction times, by lowering the temperature. Thus, the sulfoxide could be obtained in a better yield, although with a lower enantiomeric purity. The inhibition of the kinetic resolution step at 0 °C had some precedent in the literature.[22,23]

In further tests, we used cumene hydroperoxide as the oxidant, in the presence of the same titanium/hydrobenzoin complex. When the reaction was performed in toluene (Table 1, entry 9), small quantities of sulfoxide **2a** were obtained with a lower enantiomeric purity (20% yield, 53% ee), accompanied by rather large amounts of sulfone **3a** (50%) that, at variance with the previous reactions, was produced to a significant extent even with an early reaction time. A low ee value for sulfoxide **2a** (32% ee) was obtained, when the same reaction was performed in carbon tetrachloride (Table 1, entry 10). Due to this result, the use of this oxidant was abandoned.

Finally, we performed the oxidation of **1a** with TBHP in the presence of a complex between titanium and (*R*,*R*)-hydrobenzoin (Table 1, entry 11), according to the reaction conditions of entry 7, that should lead to a fair balance between isolated yield and enantioselectivity. The enantiomeric (−)-**2a** was obtained with 50% yield and 94% ee.

Further experiments were performed by using a different Sulindac sulfide alkyl ester. For this purpose, we decided to oxidise the Sulindac sulfide *tert*-butyl ester **1b**, in which a larger alkyl group was present, to obtain sulfoxide **2b**.[24] We observed a reactivity similar to the behaviour of methyl ester **2a**. When the reaction was performed in toluene (Table 1, entry 12), sulfoxide (+)-**2b** was obtained with a slight increase of enantioselectivity (49% yield, 94% ee) with respect to the reaction of **1a** in the same solvent. The corresponding sulfone **3b** was also present in this reaction. A similar trend (Table 1, entry 13) was observed when the reaction was repeated in carbon tetrachloride (48% yield, 95% ee). If this reaction was stopped after 6 h (Table 1, entry 14), sulfoxide **2b** was produced in a slightly higher isolated yield (54%), but in lower enantiomeric purity (76% ee). Thus, the presence of sulfone **3b** and the increase of the ee values of sulfoxide **2b** with time suggest that a two step mechanism (enantioselective oxidation/kinetic resolution) was also active in the asymmetric synthesis of Sulindac *tert*-butyl ester. The use of (*R*,*R*)-hydrobenzoin (Table 1, entry 15), as expected, yielded the enantiomeric sulfoxide (−)-**2b** with the same yields and ee values as the (+)-counterpart.

As far as the configurations of the Sulindac alkyl esters are concerned, sulfoxides (+)-**2a** and (+)-**2b** were obtained by the TBHP-oxidation, when (*S*,*S*)-hydrobenzoin was used as a ligand of titanium. Sulfoxide (+)-**2a** (95% ee) was treated with 1 M sodium hydroxide ethanol/water solution[1] leading to (+)-Sulindac in an almost quantitative yield (98%) and without the loss of enantiomeric excess (95% ee, as determined by NMR, upon addition of (*R*)-3,5-dinitro-*N*-1-phenylethyl)benzamide). Since the (*R*)-configuration was attributed to (+)-Sulindac,[7–11] the (*R*)-configuration should also be attributed to esters (+)-**2a** that originated in the (+)-acid. As a further confirmation, an enantioenriched mixture of (+)-**2a** or (+)-**2b** was treated with (*R*)-(methoxy)phenylacetic acid, according to a model[25] that we had previously used.[14,15] Since the methyl signal of the more abundant enantiomer showed upfield shift, the (*R*)-configuration was confirmed.

Sulindac methyl ester **2a**: mp 86–88 °C (*n*-hexane/ethanol). (*R*)-**2a** $[\alpha]_D^{25} = +61.5$ (c 1.0, $CHCl_3$) for a 96% ee sample. (*S*)-**2a** $[\alpha]_D^{25} = -60.4$ (c 1.0, $CHCl_3$) for a 94% ee sample. Sulindac *tert*-butyl ester **2b**: mp 47–49 °C (*n*-hexane/acetone). (*R*)-**2b** $[\alpha]_D^{25} = +42.2$ (c 1.0, $CHCl_3$) for a 95% ee sample. (*S*)-**2b** $[\alpha]_D^{25} = -42.8$ (c 1.0, $CHCl_3$) for a 96% ee sample. Sulindac: mp 174–176 °C (*n*-hexane/ethyl acetate). (*R*)-Sulindac $[\alpha]_D^{25} = +56.6$ (c 0.5, CH_3OH) for a 96% ee sample.

3. Conclusion

The results reported herein show that by using the appropriate reagent, catalyst, solvent and reaction conditions, the preparation of both enantiomers of Sulindac alkyl esters could be achieved with high ee values (94–96% ee) and in satisfactory isolated yield (48–50%) by a straightforward and effective synthetic strategy, without resorting to difficult or low-yielding reactions.

Moreover, the reactivity picture that emerged from the present work was as equally interesting as the synthetic aspects. As mentioned in Table 1, if Sulindac sulfide alkyl esters were oxidised by controlling the reaction time or reaction temperature, that is, in reaction conditions that were able to inhibit the formation of large amounts of sulfone, Sulindac alkyl esters were produced in higher yields but in lower enantioselectivities (54–64% yields, 71–77% ee). These results were similar to those reported for the oxidation of a simple aryl methyl sulfide (58–63%

yield, 69–80% ee),[22] under analogous reaction conditions (0 °C, 2 h reaction time). Thus, Sulindac sulfide alkyl esters, that is, large molecules bearing various functional groups, behaved similarly to small aryl methyl sulfides.

Furthermore, from the present and past investigations, the mechanism of the asymmetric oxidation of sulfides in the presence of a complex between titanium and hydrobenzoin seems to be substrate sensitive. In the first case, a genuine enantioselective oxidation occurs, as observed in the preparation of aryl benzyl sulfoxides[14] or aryl β-ketosulfoxides.[15] High ee values and high yields, due to the presence of only negligible amounts of the corresponding sulfone, are obtained. Thus, it is useless to perform the reaction at 0 °C, or with a short reaction time, since the over-oxidation of the sulfoxide is marginal, even at longer reaction times. On the other hand, enantioselective oxidation of the alkyl aryl sulfide (simple, as aryl methyl sulfide[22] or complex, as Sulindac sulfide alkyl esters) follows a two-step mechanism (enantioselective oxidation/kinetic resolution). Better ee values require that the presence of the sulfone has to be accepted, together with a consequent decrease of the isolated yields of the target optically active sulfoxide.

Even if more work on this topic seems to be needed, the mechanistic observations collected herein depicted a preliminary reactivity framework that should be useful in future application of this oxidation system to the synthesis of other bioactive chiral sulfoxides.

Acknowledgements

This work was financially supported, in part, by the MIUR Rome (National Project 'Stereoselezione in Sintesi Organica. Metodologie e Applicazioni'), by the FIRB project ('Progettazione, preparazione e valutazione biologica e farmacologica di nuove molecole organiche quali potenziali farmaci innovativi') and by the Ministero della Salute-Regione Puglia project ('Farmacoprevenzione nei pazienti con mieloma multiplo. Inibizione dell'angiogenesi e della crescita tumorale con inibitori della COX-2'). Thanks are due to Dr. Nicola Caldarola for preliminary works.

References

1. Jones, H. U.S. Patent 3,869,507, 1975; Jones, H. U.S. Patent 3,868,415, 1975.
2. Jung, M.; Wahl, A. F.; Neupert, W.; Geisslinger, G.; Senter, P. D. *Pharm. Pharmacol. Commun.* **2000**, *6*, 217–221.
3. Duffy, C. P.; Elliott, C. J.; O' Connor, R. A.; Heenan, M. M.; Coyle, S.; Cleary, I. M.; Kavanagh, K.; Verhaegen, S.; O' Loughlin, C. M.; NicAmhlaoibh, R.; Clynes, M. *Eur. J. Cancer* **1998**, *34*, 1250–1259.
4. Piazza, G. A.; Kulchak Rahm, A. L.; Krutzsch, M.; Sperl, G.; Paranka, N. S.; Gross, P. H.; Brendel, K.; Burt, R. W.; Alberts, D. S.; Pamucku, R.; Ahnen, D. J. *Cancer Res.* **1995**, *55*, 3110–3116.
5. Jung, B.; Barbier, V.; Brickner, H.; Welsh, J.; Fotedar, A.; McClelland, M. *Cancer Lett.* **2005**, *219*, 15–25.
6. Baldwin, G. S.; Rorison, K. A. *Biochim. Biophys. Acta* **1999**, *1428*, 68–76.
7. Maguire, A. R.; Papot, S.; Ford, A.; Touhey, S.; O' Connor, R.; Clynes, M. *Synlett* **2001**, 41–44.
8. Korte, A.; Legros, J.; Bolm, C. *Synlett* **2004**, 2397–2399.
9. Light, D. R.; Waxman, D. J.; Walsh, C. *Biochemistry* **1982**, *21*, 2490–2498.
10. Hamman, M. A.; Haehner-Daniels, B. D.; Wrighton, S. A.; Rettie, A. E.; Hall, S. D. *Biochem. Pharmacol.* **2000**, *60*, 7–17.
11. Bolm, C.; Muñiz, K.; Hildebrand, J. P. Oxidations of Sulfides. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfalz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 697–710.
12. Legros, J.; Dehli, J. R.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 19–31.
13. Capozzi, M. A. M.; Cardellicchio, C.; Naso, F. *Eur. J. Org. Chem.* **2004**, 1855–1863.
14. Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Rosito, V. *J. Org. Chem.* **2002**, *67*, 7289–7294.
15. Cardellicchio, C.; Hassan Omar, O.; Naso, F.; Capozzi, M. A. M.; Capitelli, F.; Bertolasi, V. *Tetrahedron: Asymmetry* **2006**, *17*, 223–229.
16. Seto, M.; Miyamoto, N.; Aikawa, K.; Aramaki, Y.; Kanzai, N.; Iizawa, Y.; Baba, M.; Shiraishi, M. *Bioorg. Med. Chem.* **2005**, *13*, 363–386.
17. Meneghin, M. European Patent EP0206241, 1986.
18. Sperl, G.; Gross, P.; Pamucku, R.; Brendel, K.; Piazza, G. A. U.S. Patent 6,071,934, 2000.
19. Drago, C.; Caggiano, L.; Jackson, R. F. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 7221–7223.
20. Kelly, P.; Lawrence, S. E.; Maguire, A. R. *Synlett* **2006**, 1569–1573.
21. Kelly, P.; Lawrence, S. E.; Maguire, A. R. *Eur. J. Org. Chem.* **2006**, 4500–4509.
22. Donnoli, M. I.; Superchi, S.; Rosini, C. *J. Org. Chem.* **1998**, *63*, 9392–9395.
23. Jia, X.; Li, X.; Xu, L.; Li, Y.; Shi, Q.; Au-Yeung, T. T.-L.; Yip, C. W.; Yao, X.; Chan, A. S. C. *Adv. Synth. Catal.* **2004**, *346*, 723–726.
24. Hinkley, D.; Conn, J. U.S. Patent 3,732,292, 1973; Chemerda, J. M.; Pines, S. H. Swiss Patent CH 615418, 1980.
25. Buist, P. H.; Marecak, D.; Holland, H. L.; Brown, F. M. *Tetrahedron: Asymmetry* **1995**, *6*, 7–11.