Pergamon

Tetrahedron Letters 40 (1999) 3293–3296

TETRAHEDRON LETTERS

An Efficient Asymmetric Catalytic Hydrogenation of 4-Aryl Coumarins, Preparation of a Key Intermediate in the Synthesis of a Class of Endothelin Receptor Antagonists

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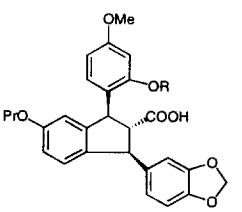
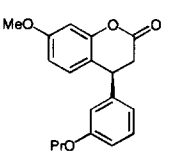
Received 4 December 1998; revised 22 February 1999; accepted 24 February 1999

Abstract: The 4-aryl-3,4-dihydrocoumarin **1** is a critical intermediate in the synthesis of two endothelin receptor antagonists. Asymmetry is introduced by the chiral catalytic hydrogenation of **2**. Reduction occurs only if the lactone is open (**3**). A number of chiral ruthenium and rhodium organometallic species are evaluated as catalysts. The reaction is optimized to produce **1** in high yield and *ee*.

SB 209670 and SB 217242 are endothelin antagonists currently under development by SmithKline Beecham. A number of physiological responses are mediated by endothelin receptors. By blocking these receptors it is hoped that certain detrimental human physiological responses can be controlled.[1] An efficient racemic route towards these compounds employs as a key intermediate the dihydrocoumarin **1**.[2] An enantioselective approach to these molecules was developed using the *S*-enantiomer of **1**. There are several enantioselective approaches to this class of molecule in the literature, but no approach was suitable for manufacturing scale.[3] It seemed likely that chirality could be induced in this molecule through the catalytic hydrogenation of the readily available coumarin **2**.[4] A large and developing body of literature exists on the asymmetric hydrogenation of olefins using ruthenium and rhodium catalysts.[5]



SB 209670: R = CH_2COOH
SB 217242: R = CH_2CH_2OH



1

For the initial experiments, [(*S*)-(–)-2,2'-bis(diphenylphospino)-1,1'-binaphthyl]chloro(*p*-cymene) ruthenium chloride was employed as the catalyst.[6] No reduction of **2** was observed in methanol at 50 °C and 80 psi H_2. Upon further consideration of the substrate, it was recognized that **2** did not conform to the normal "rules" for chiral hydrogenation.[7] The ring was too rigid and perhaps sterically hindered. However, if the lactone were opened to **3**, two sites in the same vicinity, a phenol oxygen and a carbonyl oxygen, would be available for catalyst binding and the substrate would be flexible. In practice, opening the lactone ring proved to be successful. Addition of aqueous base to the reaction mixture under identical conditions resulted in complete hydrogenation within 18 h. The open compound **4** gradually lactonized upon standing, but could be more readily transformed to **1** by heating in the presence of *p*-toluenesulfonic acid. The resultant product was obtained with a 65% *ee* (entry 1).

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PII: S0040-4039(99)00478-5

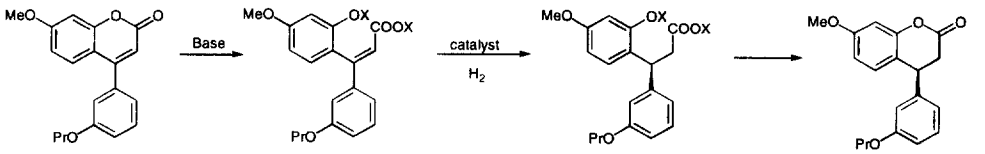


Table 1. Reaction Conditions for the Chiral Hydrogenation of **2** to **1**

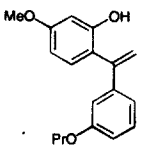
entry	catalyst	base	solvent	temp	pressure	*ee*
1	[RuCl(*S*-BINAP)(*p*-cymene)]Cl	NaOH	MeOH	50 °C	80 psi	65%
2	[RuCl(*S*-BINAP)(*p*-cymene)]Cl	LiOH	MeOH	50 °C	80 psi	64%
3	[RuCl(*S*-BINAP)(*p*-cymene)]Cl	KOH	MeOH	50 °C	80 psi	44%
4	[RuCl(*S*-BINAP)(*p*-cymene)]Cl	*n*-Bu_4NOH	MeOH	50 °C	80 psi	65%
5	[RuCl(*S*-BINAP)(*p*-cymene)]Cl	NaOH	IPA	50 °C	80 psi	39%
6	[RuCl(*S*-BINAP)(*p*-cymene)]Cl	NaOH	$MeOH/CH_2Cl_2$	25 °C	80 psi	46%
7	[RuCl(*S*-BINAP)(*p*-cymene)]Cl	NaOH	MeOH	50 °C	3 psi	85%
8	[RuCl(*S*-*p*-tol-BINAP)(*p*-cymene)]Cl	NaOH	MeOH	50 °C	3 psi	84%
9	$RuBr_2$(*S*-*p*-tol-BINAP)	NaOH	MeOH	50 °C	10 psi	64%
10	[Rh(COD)(*S,S*-di-Et-Duphos)]triflate	NaOH	MeOH	50 °C	400 psi	78%
11	[Rh(NBD)(*R*-Prophos)]ClO_4[8]	NaOH	MeOH	50 °C	400 psi	43%
12	[Rh(NBD)(*S,S*-Skewphos)]ClO_4[9]	NaOH	MeOH	50 °C	400 psi	44%
13	[Rh(NBD)(*S,S*-Chiraphos)]ClO_4[10]	NaOH	MeOH	50 °C	400 psi	85%
14	1:2 $[Rh(COD)Cl]_2$:*S,S*-Chiraphos	NaOH	MeOH	50 °C	180 psi	95%
15	1:2 $[Rh(COD)Cl]_2$:*S,S*-Chiraphos	NaOH	MeOH	50 °C	80 psi	91%

Table 1 details changes in reaction parameters with resultant enantioselectivity. Two equivalents of base optimized reaction rate and enantioselectivity. Slightly elevated temperatures (40–50 °C) were necessary to solubilize **2** and ensure that lactone opening to **3** proceeded at a suitable rate. Higher temperatures (60 °C) were undesirable due to the formation of by-product **5** [11], which did not reduce under the reaction conditions. The formation of **5** was presumably a base catalyzed effect. Complete conversion to **5** was observed under the reaction conditions even when both catalyst and hydrogen were left out. Pressure was the most significant variable affecting *ee*[12]; the best selectivity was obtained at 1-5 psi. Combining all these variables (entry 7), yields of 85% and enantiomeric excesses of 84% were consistently achieved in fixed equipment on scales of 30-65 g.

A problem with the [(*S*)-BINAP (*p*-cymene)(Cl)Ru]Cl system was that a relatively high catalyst loading (1.4 mol %) was necessary to achieve >97% conversion. At lower loadings, yields dropped and the buildup of **3** and **5** was observed. Enantioselectivity however, was unchanged. This high loading adversely affected the cost of the process, initiating a search for a more effective catalyst (entries 10-15).

A significant improvement in the process was achieved with use of an '*in-situ*' catalyst system comprised of a 1:2 molar mixture of $[Rh(COD)Cl]_2$ and *S,S*-Chiraphos (entries 14-15).[13] Under identical reaction conditions, catalyst loadings as low as 0.1 mol % gave **1** in unprecedented 94-96% *ee* with good yields (85-90%).[14,15] Problems of catalyst oxygen stability were thus avoided by substituting two components of long term stability. A multi-step catalyst synthesis was eliminated as well, offering a more efficient use of expensive rhodium and chiral phosphine components. Using this system, 500 g quantities of **2** were consistently hydrogenated with 90% yield and 94% *ee*.[16]

This methodology could be extended to other 4-aryl-coumarin analogs such as **6**. An 84% yield and an 84% *ee* were obtained using [Rh(NBD)(*S*,*S*-Chiraphos)]ClO_4 as catalyst. However, **7** did not reduce under standard reaction conditions, presumably as the catalyst bound preferentially to the less hindered phenol.



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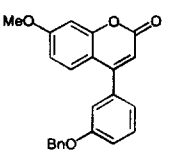

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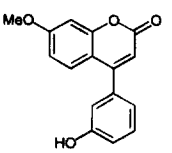
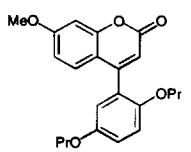


7

Substitution on the 4-aryl group played a significant role in both the reactivity of the substrate and the enantioselectivity of the final product. The reduction of **8** [((*S*)-BINAP)(*p*-cymene)(Cl)Ru]Cl, 5 psi H_2, 50 °C) proceeded sluggishly, requiring twice the normal catalyst loading (2.85%) and long reaction times (48 h) to proceed to completion. An 84% *ee* was obtained, but surprisingly of the opposite isomer **9**.



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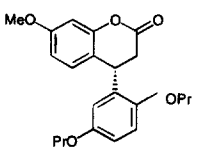

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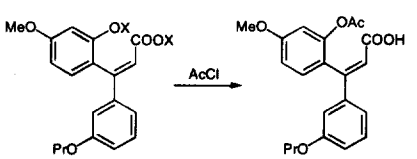

3 **10**

Both the phenolic and the carboxylic catalyst binding sites appear to be necessary for chiral hydrogenation to occur. As mentioned, **5** does not reduce with these catalysts. The phenolic position was acylated to produce **10**, which did not reduce using [((*S*)-BINAP (*p*-cymene)(Cl)Ru]Cl even at high pressures (400 psi H_2).

In conclusion, we have discovered an efficient, economical chiral catalyst system for the synthesis of the chiral dihydrocoumarin **1**. The reduction was successful on a large scale with both high yield and enantioselectivity. In a short sequence, **1** can be converted to either endothelin receptor antagonist, SB 209670 or SB 217242, to provide material of high enantio-purity.

Acknowledgment. We thank Larry Gillyard for his help in the high-pressure laboratory.

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11. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, J = 7.4 Hz, 3 H), 1.77-1.83 (m, 2 H), 3.82 (s, 3 H), 3.90 (t, J = 6.5 Hz, 2 H), 5.26 (s, 1 H), 5.37 (d, J = 1.2 Hz, 1 H), 5.78 (d, J = 1.2 Hz, 1 H), 6.49-6.52 (m, 2 H), 6.89-6.96 (m, 3 H), 7.04-7.07 (m, 1 H), 7.22-7.28 (m, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 10.56, 22.60, 55.32, 69.53, 101.21, 106.75, 113.61, 114.49, 116.17, 119.59, 120.16, 129.65, 131.14, 141.40, 145.20, 154.34, 159.41, 160.80.
12 Sun, Y.; Landau, R. N.; Wang, J.; LeBlond, C.; Blackmond, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 1348.
13. Reactor cleanliness was essential to achieve high enantioselectivity. Residual hydrogenation could still occur in a 'visually clean' vessel, lowering *ee* values. This was particularly true if the reactor had previously been used for heterogeneous catalysis. A two step cleaning procedure was routinely performed prior to each reaction. The vessel was first treated with 10% HCl at 50 °C for 2-4 h. Then a solution of maleic acid in methanol (1 g/10 mL) was run at 50 °C and 300 psi hydrogen for 2-6 h. After this time, a sample of the methanol solution was examined by ^{1}H NMR for evidence of hydrogenation. The maleic acid procedure was repeated until no hydrogenation was observed.
14. The progress of the hydrogenation and subsequent transformations could be followed by chromatographic analysis using an HP Hypersil ODS column (5 μ, 200 x 4.6 mm) with 60:40:0.1 acetonitrile:water:acetic acid as eluent at a flow rate of 1.0 mL/min and detection at 230 nm. The following retention times were observed: **2**-16.3 min, **1**-12.6 min, **3**-4.6 min, **4**-4.2 min.
15. The enantiomeric excess of **1** was determined by chromatographic analysis on a Chiralpak AD column (Chiral Technologies) using 95:5 hexane:2-propanol as the mobile phase at a flow rate of 1.0 mL/min and detection at 275 nm. The retention times of **1** (*S*-isomer) and **1** (*R*-isomer) were 12.6 min and 11.4 min respectively.
16. **3,4-Dihydro-7-methoxy-4-(*S*)-4-(3-propoxyphenyl)-2*H*-1-benzopyran-2-one (1).** A clean[13] 100 mL stainless steel autoclave was charged with **2** (7.75 g, 25.0 mmol), abs. methanol (69 mL), 4 N NaOH (12.5 mL, 50.0 mmol, 2 eq) and one of the following catalyst systems: a) [(*S*)-BINAP(*p*-cymene)(Cl) Ru]Cl (325 mg, 0.35 mmol, 1.4%); b) [Rh(NBD)(*S*-Chiraphos)]ClO_4 (36 mg, 0.05 mmol, 0.2%); c) $[Rh(COD)Cl]_2$ (6.2 mg, 0.0125 mmol, 0.05%) and *S,S*-Chiraphos (10.7 mg, 0.025 mmol, 0.1%). The sealed vessel was purged several times with nitrogen and hydrogen. The stirred reaction was run at 50 °C for 18–24 h under the appropriate hydrogen pressure [((*S*)-BINAP)(*p*-cymene)(Cl)Ru]Cl: 1-5 psi; [Rh(NBD)(*S*-Chiraphos)]ClO_4: 400 psi; $[Rh(COD)Cl]_2$ and *S,S*-Chiraphos: 180 psi). The reaction mixture was cooled and removed from the vessel. The methanol solution was concentrated *in vacuo* to near dryness. The residual brown oil was dissolved in water (100 mL) and washed with toluene (2 x 50 mL). The toluene phases were combined and washed with 1 N NaOH (30 mL). The 1 N NaOH wash was combined with the original aqueous phase. This was acidfied to pH 1–2 with 6 N HCl (20 mL) and extracted with toluene (3 x 150 mL). The combined toluene extracts were washed with brine (150 mL), dried over magnesium sulfate (10 g), filtered, and concentrated *in vacuo* to approximately one half the original volume.

    The toluene solution was treated with *p*-toluenesulfonic acid monohydrate (2.0 g) and heated to 50 °C for 1 h, or until HPLC indicated that lactonization was complete.[14] The solution was cooled, washed with brine (100 mL), dried over magnesium sulfate (10 g), filtered, slurried with florisil (10 g) for 15 min, filtered, and concentrated *in vacuo* to near dryness as a clear oil. Addition of hexanes (50 mL) to the stirred oil resulted in a white filterable solid of **1** (6.63 g, 85% yield). Chiral HPLC[15] indicated 94-96% *ee*. mp 70-72 °C. $[\alpha]_D^{25}$ = 25.4 (c 1.0 $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J = 7.4 Hz, 3 H), 1.73-1.84 (m, 2 H), 2.99-3.04 (m, 2 H), 3.80 (s, 3 H), 3.86-3.90 (m, 2 H), 4.22-4.26 (m, 1 H), 6.61-6.90 (m, 5 H), 7.21-7.27 (m, 2 H). ^{13}C NMR ($CDCl_3$) δ 10.51, 22.55, 37.20, 40.09, 55.53, 69.47, 102.49, 110.74, 113.14, 114.10, 117.53, 119.57, 128.96, 130.07, 142.34, 152.43, 159.65, 159.98, 167.73. FT-IR (KBr) 1763, 1627, 1609, 1583, 1265, 1218, 1158, 1125, 870, 835, 825, 781 cm^{-1}.