Pergamon

Tetrahedron Letters 40 (1999) 2187–2190

TETRAHEDRON LETTERS

Stereoselective Synthesis of a Candoxatril Intermediate via Asymmetric Hydrogenation.

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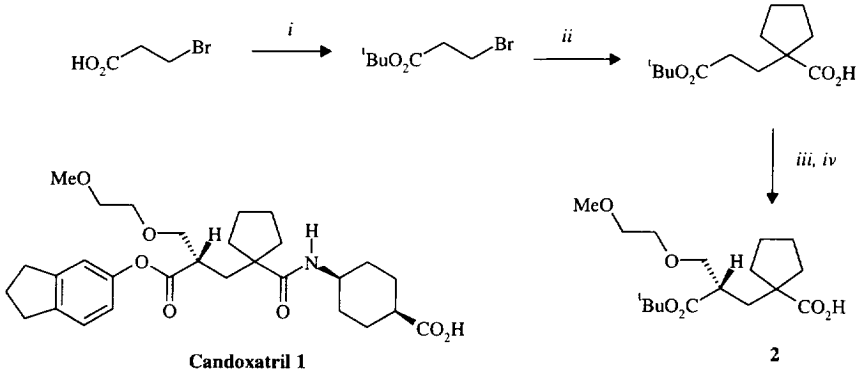
Received 25 November 1998; accepted 21 December 1998

Abstract: A four step synthesis of a chiral glutarate half ester intermediate, required for the preparation of candoxatril, has been developed from t-butyl acrylate. The key steps in this route include a stereoselective synthesis of a trisubstituted alkene and its asymmetric hydrogenation with a Ru-BINAP catalyst.

Candoxatril (**1**) [1,2] is an orally active inhibitor of the zinc metalloprotease neutral endopeptidase EC 3.4.24.11 which is involved in the metabolic inactivation of the peptide hormone atrial natriuretic factor (ANF). It potentiates the natriuretic actions of ANF in animals and man and has demonstrated clinical efficacy for the treatment of congestive heart failure [3]. The substituted chiral glutarate half ester **2** is a key intermediate in the preparation of candoxatril and was originally prepared by the four step synthetic route shown in Scheme 1 [4]. The chiral (*S*)-enantiomer was produced by classical resolution of the racemate with (*1S,2S*)-(+)-pseudoephedrine to give **2** in 13% overall yield from commercially available 3-bromopropionic acid.

Scheme 1



Candoxatril 1 **2**

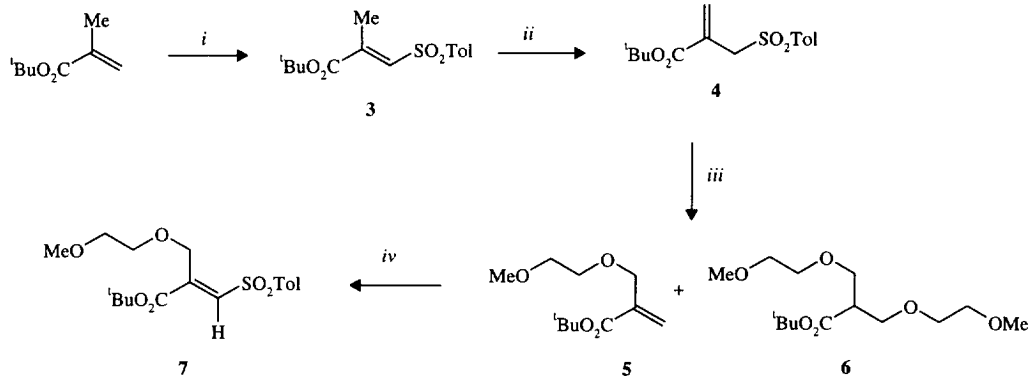
Reaction conditions: (*i*) isobutylene, H_2SO_4, t-BuOH, -20°C, 97%; (*ii*) 1). cyclopentanecarboxylic acid (1.0 eq), i-Pr_2NLi (2.2eq), THF, -20°C to r.t., 2h; 2). t-butyl 3-bromopropionate (1.1 eq), -10°C to r.t., 16h, 40%; (*iii*) 1. i-Pr_2NLi (2.0eq), THF, -65°C, 1.5h; 2. 2-methoxyethoxymethyl chloride (MEMCl) (1.1 eq), -78°C to r.t., 83%; (*iv*) (1S,2S)-(+)-pseudoephedrine, n-hexane, 40%.

Although this synthesis was concise, it suffers from the inherent inefficiency of a classical resolution, the use of hazardous reagents (MEMCl) and poor overall yield. We required a cost effective enantioselective route to **2** since the enzyme inhibitory activity of candoxatril resides primarily in the (*S*)-enantiomer. Herein, we describe a four step synthesis of **2** that exploits an enantioselective asymmetric hydrogenation as the key step. It was envisaged that a potential asymmetric hydrogenation substrate [5] could be accessed in a stereoselective

0040-4039/99/$ - see front matter
PII: S0040-4039(98)02687-2

manner, by the conjugate addition of a metallated derivative of cyclopentanecarboxylic acid (CPA) to a suitably substituted acrylate. We selected β-tosyl acrylate **7** (Scheme 2) on the basis of ease of preparation and literature precedent for similar compounds being used as β-acylvinyl cation equivalents [6]. The literature also suggested that conjugate addition to **7** was likely to be a stereoselective process which would allow access to a single geometrical isomer of the asymmetric hydrogenation substrate. To establish the viability of this approach, a synthesis of **7** was initially developed from commercially available t-butyl methacrylate (Scheme 2).

Scheme 2



Reaction conditions: (*i*) 1. I_2 (1.0 eq), $CH_3C_6H_4SO_2Na.2H_2O$ (1.0 eq), CH_2Cl_2, r.t., 24h; 2. Et_3N (1.5 eq), 0°C, 15 min, r.t., 3h; (*ii*) Et_3N (1.5 eq), EtOAc, reflux, 8h, 63% (steps *i* and *ii*); (*iii*) K_2CO_3 (2.0 eq), $MeO(CH_2)_2OH$, 0°C, 3h, 84%; (*iv*) 1. p-TsI (1.5 eq), CH_2Cl_2, r.t., 16h; 2. Et_3N (2.0 eq), r.t., 3.5h, 90%.

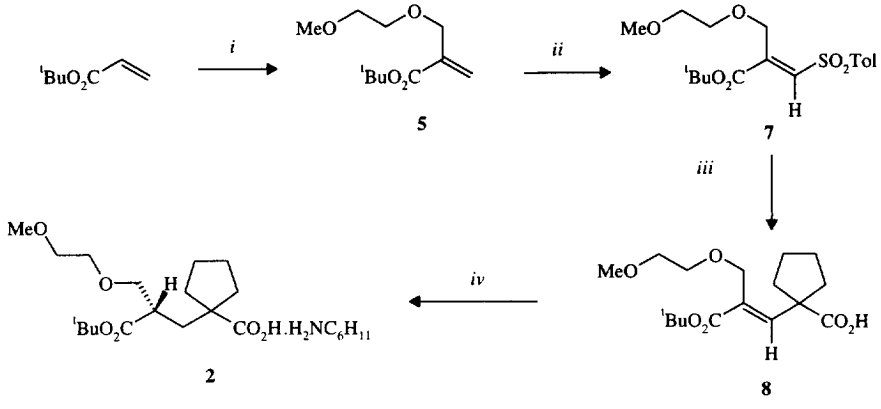
Functionalisation of the methyl group of t-butyl methacrylate was achieved using the tandem iodosulfonation-dehydroiodination sequence reported by Najera and Yus [7,8]. This provided vinyl sulfone **3** which was readily isomerised to the thermodynamically more stable allylic isomer **4** (63% overall yield after chromatography). Treatment of allylic sulfone **4** with potassium carbonate in dry 2-methoxyethanol gave the desired ether **5** and up to 10% of the bis-addition product **6** which was readily removed by chromatography. The synthesis was completed with a second iodosulfonation-dehydroiodination sequence to give (E)-**7** in 90% yield. Higher yields of product were obtained in this reaction when pre-formed p-toluenesulfonyl iodide was used instead of the *in situ* preparation method [7]. The (E)-stereochemistry of **7** was confirmed by a single crystal X-ray analysis [9].

A more efficient single step synthesis of acrylate **5** has also been developed from inexpensive t-butyl acrylate (Scheme 3) using the Baylis-Hillman reaction [10]. Employing optimised conditions, a mixture of t-butyl acrylate, paraformaldehyde and 3-quinuclidinol catalyst [11] were heated to 65-70°C in dry 2-methoxyethanol for 48h to give the desired acrylate **5** in 72% yield after chromatography. This reaction proceeds through a hydroxymethyl acrylate intermediate which is transformed to the product under the reaction conditions. It has been suggested that this unusually facile ether formation proceeds by way of an ene-type mechanism involving a six-membered transition state [12]. The considerably less expensive catalyst 1,4-diazabicyclo[2.2.2]octane (DABCO) could also be used for this reaction in place of 3-quinuclidinol, however 1.75 equivalents of this base and a temperature of 100°C were required to achieve a comparable yield of **5**.

With the desired β-tosyl acrylate **7** in hand, we next investigated addition reactions with metallated derivatives of CPA [13]. The addition of the lithiodianion of CPA to acrylate **7**, with or without additives e.g. TMEDA, gave a complex mixture of products and a low yield of the desired product **8**, a major side reaction surprisingly being 1,2-addition to the t-butyl ester. Previous work at Pfizer [14] indicated that the addition of zinc chloride to the lithiodianion of CPA has a dramatic effect on reactivity and yield in 1,4-addition reactions to acrylates. This modification proved effective in the case of substrate **7**. Addition of an ethereal solution of zinc chloride (0.6 eq) to the lithiodianion of CPA in THF (0°C, 30 min) followed by **7** (-10 to 0°C, 4h) gave the desired hydrogenation substrate **8** in 76% yield after chromatography. The reaction is highly stereoselective and

proceeds with retention of configuration. The (*E*)-stereochemistry of **8** was assigned from a combination of a comparison of chemical shift, nOe and C-H coupling constant data [15].

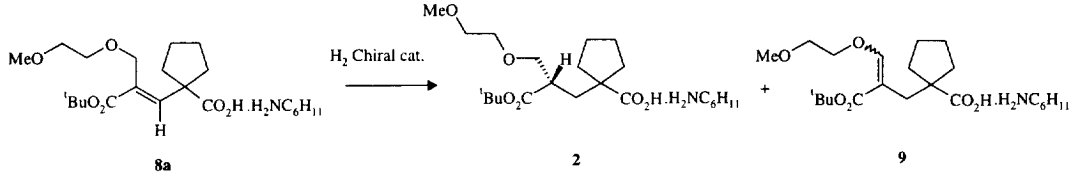
Scheme 3



Reaction conditions: (*i*) H_2CO (1.5 eq), 3-quinuclidinol (0.5 eq), $MeO(CH_2)_2OH$, 65-70°C, 48h, 72%; (*ii*) 1) p-TsI (1.5 eq), CH_2Cl_2 r.t., 16h; 2) Et_3N (2.0 eq), r.t., 3.5h, 90%; (*iii*) CPA (1.0 eq), i-Pr_2NLi (2.2eq), THF, 0°C to r.t., 2h, $ZnCl_2$ (0.6 eq), 0°C, 30min; 2. **7** (1.0 eq) -10°C to 0°C, 4h, 76% after chromatography; (*iv*) 1. [(R)-BINAP(p-cymene)RuCl]Cl (0.01%), MeOH//H_2O (3:1), H_2 (60 p.s.i), 45-50°C, 16h.

The addition of zinc chloride increases the solubility of the dianion and markedly reduces its reactivity. In contrast to the lithiodianion, the reaction of **7** with the zinc modified dianion was found to be very slow below -10°C. It is postulated that zinc chloride reduces the basicity of the dianion and it may also activate the sulfone group to displacement. With the trisubstituted alkene **8** in hand, we next investigated the key asymmetric hydrogenation reaction with a series of commercially available chiral ligands and catalysts [16]. Initial results with the free acid were not encouraging, therefore a crystalline cyclohexylamine salt **8a** (m.p 120-122°C) was prepared for this study to increase binding to the catalyst. The results of initial catalyst screening studies are shown in Table 1.

Table 1 Asymmetric hydrogenation of **8a** with commercially available chiral ligands and catalysts.



Entry	Catalyst[a]	Conf	ee [%] [b]	**2:9**[c]
1	$[Rh(COD)Cl]_2$ + (+)-DIOP	R	24	100:0
2	$[Rh(COD)Cl]_2$ + (R)-PROPHOS	S	8	100:0
3	$[Rh(COD)Cl]_2$ + (S,S)-BPPM	S	22	100:0
4	$[Rh(COD)Cl]_2$ + (S)-BINAP	S	78	100:0
5	[Rh(COD)-(R)-BINAP]ClO_4	R	80	100:0
6	RuHCl[(S)-BINAP]$_2$ [18]	R	82	92:8
7	RuCl[R-BINAP](p-cymene)]Cl [19]	S	94	75:25

[a] conditions: substrate to catalyst ratios (S/C) 35 to 1,000:1; 15 to 60 p.s.i H_2; c =0.1 to 0.4 M MeOH (entry 1 Toluene/EtOH 1:2, entry 7 MeOH/H_2O 3:1); temperatures r.t. to -50°C; [b] ee's were determined by chiral HPLC [17]; [c] ratio of **2** to **9** was determined by ^1H NMR.

Of the chiral phoshines examined, only catalysts containing the BINAP ligand showed significant enantioselectivity. Hydrogenation of **8a** with a rhodium-(S)-BINAP catalyst (Table 1, entry 4), prepared by the *in situ* addition of diphosphine to chloro(1,5-cyclooctadiene)rhodium(I) dimer, gave **2** in 78% ee (S/C 40:1, 15 p.s.i H_2, 40-45°C). Attempts to increase the substrate to catalyst ratio by increasing the hydrogen pressure led to a reduction in enantioselectivity (50 p.s.i, 68% ee). Increasing the reaction temperatures above 55-60°C resulted in decarboxylation of the substrate. In contrast the cationic ruthenium arene catalyst (Table 1, entry 7) showed increased catalytic activity and hydrogenated **8a** (94% ee, 50g scale) within 24h using substrate to catalyst ratios of up to 1,000:1 (0.001 mole %). The sense of asymmetric induction for the ruthenium catalysts (entries 5 and 6) was opposite to the rhodium catalyst (entry 4) for a given BINAP enantiomer. A significant competing side reaction (20-25%) with the ruthenium catalysts was isomerisation to a mixture of enol ethers **9** (Z:E 2.5:1) which are not reduced under the reaction conditions. The enol ethers were effectively purged and the optical purity upgraded by crystallisation from ethyl acetate/hexane to give **2** (cyclohexylamine salt) in 68% yield. The ruthenium catalyst was selected for scale-up on economic grounds and the synthesis developed into a chromatography-free potential manufacturing process in collaboration with our industrial partners PPG-SIPSY and Robinson Brothers Ltd.

In summary, an efficient four step asymmetric synthesis (33% overall yield) of the candoxatril intermediate **2** has been developed from t-butyl acrylate which avoids the use of hazardous MEMCl. The key step in this synthesis involves asymmetric hydrogenation of the trisubstituted alkene **8** with a ruthenium (II) catalyst containing the (R)-BINAP ligand.

Acknowledgements: We would like to thank Dr Mike Williams and Professor Steve Ley for their helpful discussions. We also thank Jean Lastennet (PPG-SIPSY), Steve Ray, Jolyon Perkins and Phil Ferguson (Pfizer) for their involvement in the development of this route into a manufacturing process.

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