

Tetrahedron Letters 40 (1999) 8667-8670

TETRAHEDRON LETTERS

## Asymmetric synthesis of the northern segment of ephedradine C. A novel dihydrobenzo[b]furan formation

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Received 3 September 1999; accepted 28 September 1999

## Abstract

An asymmetric synthesis of the dihydrobenzo[b]furan segment of ephedradine C has been achieved utilising a chiral oxazolidinone in an aldol reaction to form a  $\beta$ -hydroxy ester, followed by a novel debenzylation and concomitant intramolecular cyclisation with iodotrimethylsilane as key steps. An asymmetric Michael reaction with a homochiral lithium amide was used to form the third and final chiral centre. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: asymmetric synthesis; benzofurans.

The ephedradines A, B, C and D (1-4) are components of the crude drug 'mao-kon', prepared from the underground parts of *Ephedra* plants, and have been used as an antiperspirant in Oriental medicine. They were all first isolated by Hikino et al.<sup>1-4</sup> who established their structures by a combination of spectroscopic studies and a single crystal X-ray analysis on the dihydrobromide salt of ephedradine A. He also demonstrated their ability to produce hypotension in rats.<sup>5</sup> The structures are characterised by a highly substituted dihydrobenzofuran nucleus which bridges a 17-membered lactam ring containing a spermine unit, with the absolute configuration at the three chiral centres being assigned as 2R,3R,17S. To date no total synthesis of any of the ephedradines has been published, although Wasserman et al.<sup>6</sup> have communicated a racemic synthesis of the related *O*-methylorantine (5). Ephedradine C (3) was selected as the initial target and herein we report the first asymmetric synthesis of the suitably functionalised dihydrobenzo[*b*]furan segment with all three chiral centres in place.

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The enantiospecific synthesis of a dihydrobenzo[b]furan unsubstituted at the C-5 position by the use of Evans aldol methodology has been previously communicated.<sup>7</sup> However, early studies aimed at introducing suitable functionality at this C-5 position, such as acetals, silvl protected alcohols and  $\alpha$ , $\beta$ -unsaturated esters, failed completely during the enantioselective aldol reaction, with some decomposition of the ring substituent usually seen. Gratifyingly, the incorporation of a versatile bromine substituent could be successfully accomplished. The required homochiral oxazolidinone (10) was readily prepared in five steps from 4-bromophenol (Scheme 1).



Scheme 1. Reagents: (i) allyl bromide,  $K_2CO_3$ , DMF, rt, 16 h; (ii) 223–230°C, 2 h; (iii) PhCH<sub>2</sub>Br,  $K_2CO_3$ , DMF, rt, 2.5 h; (iv) H<sub>5</sub>IO<sub>6</sub>, RuCl<sub>3</sub>·3H<sub>2</sub>O, MeCN–CCl<sub>4</sub>–H<sub>2</sub>O, rt, 16 h; (v) (a) Me<sub>3</sub>CCOCl, Et<sub>3</sub>N, Et<sub>2</sub>O, -78 to 0°C, 1 h; (b) (4*R*)-4-isopropyl-2-oxazolidinone, BuLi, THF, -78 to 0°C, 45 min

The enantioselective aldol reaction now proceeded in high yield and de to give the expected *erythro* isomer (11; Scheme 2). As expected, the usual<sup>7</sup> hydrogenolysis using Pd on C of 11 followed by treatment with boron trifluoride-ether complex led to the debrominated dihydrobenzofuran. However, treatment of 11 with iodotrimethylsilane (2.2 equiv.) led not only to debenzylation but also to concomitant intramolecular cyclisation to give the required *trans*-dihydrobenzo[*b*]furan (12) as a single diastereomer in good yield. As far as can be ascertained, this is a novel method of dihydrobenzo[*b*]furan ring formation.

The oxazolidinone (12) was subsequently converted into the methyl ester (13) and this underwent the Heck reaction with *tert*-butyl acrylate to give the desired functionalised dihydrobenzo[b]furan (14). Since the dihydrobenzo[b]furan is sensitive to strong base promoted ring opening, the methyl ester was hydrolysed to the acid (15) using the mild conditions of barium hydroxide in THF-MeOH. An asymmetric addition of a homochiral lithium amide (4 equiv.) to the  $\alpha$ ,  $\beta$ -unsaturated ester (15) gave the  $\beta$ -amino ester (16) with a de >98%.



Scheme 2. Reagents: (i) (a) 9-BBN triflate, *i*-Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 1 h; (b) 3,4-dimethoxybenzaldehyde,  $-78^{\circ}$ C to rt, 3 h; (ii) Me<sub>3</sub>SiI, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h; (iii) NaOMe, MeOH, 0°C, 2 h; (iv) CH<sub>2</sub>=CHCO<sub>2</sub>*t*-Bu, Et<sub>3</sub>N, Pd(OAc)<sub>2</sub>, P(*o*-tolyl)<sub>3</sub>, sealed tube, 100°C, 16 h; (v) Ba(OH)<sub>2</sub>·8H<sub>2</sub>O, THF–MeOH, rt, 1 h; (vi) BuLi, (*R*)-(+)-*N*-benzyl-1-phenylethylamine, THF,  $-78^{\circ}$ C, 2 h; (vii) H<sub>2</sub>, Pd(OH)<sub>2</sub> on C, MeOH–H<sub>2</sub>O–AcOH, 2 h

Debenzylation of adduct (16) using Pd on C in acetic acid, or with  $Pd(OH)_2$  on C in ethanol, led to low yields of deprotected material. However, the use of  $Pd(OH)_2$  on C in a three solvent system<sup>8</sup> gave good yields of deprotected amine (17), although longer reaction times led to significant cleavage of the dihydrobenzo[b]furan ring.

The expected relative stereochemistry of 17 was confirmed by a single crystal X-ray analysis.<sup>9</sup> Compound 17 contains all three chiral centres found in ephedradine C, and is suitably functionalised to allow the completion of the synthesis through introduction of the spermidine unit. This may be achievable by utilising similar chemistry to that of Wasserman et al.<sup>6</sup> who had a similar intermediate, albeit racemic, in the synthesis of  $(\pm)$ -O-methylorantine.

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