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A convenient synthesis of the paclitaxel side-chain *via* a diastereoselective Staudinger reaction

Stephen Brown,[a] Allan M. Jordan,[a] Nicholas J. Lawrence,[a]* Robin G. Pritchard[a] and Alan T. McGown[b]

a. Department of Chemistry, University of Manchester Inst. of Science and Technology, PO Box 88, Manchester, M60 1QD, UK.
b. CRC Department of Drug Development, Paterson Institute for Cancer Research, Christie Hospital NHS Trust, Wilmslow Road, Manchester, M20 4BX, UK.

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Abstract: The *N*-benzylidene derivative of (*S*)-(-)-1-(*p*-methoxyphenyl)propyl-1-amine, obtained by a new resolution procedure, exhibits moderate selectivity in the reaction with 2-acetoxyketene; the (*S*)-(-)-1-(*p*-methoxyphenyl)propyl group can be oxidatively cleaved from the resultant β-lactam, an important precursor for taxane semi-synthesis. © 1998 Elsevier Science Ltd. All rights reserved.

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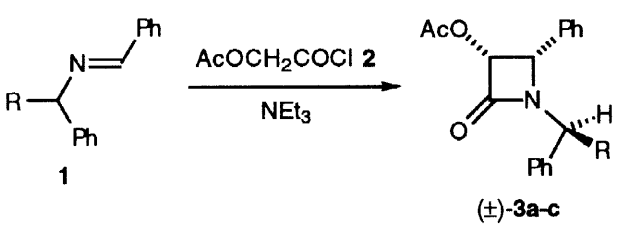
The current interest in the anticancer drug paclitaxel has led to the need for good synthetic routes to the C-13 side chain. In all the total syntheses reported to date the side-chain has been installed as one of the late steps.[1] More importantly the side-chain is used in the commercial semi-synthetic production of paclitaxel from the natural precursor 10-deacetylbaccatin-III. The side-chain is also a very important structural feature[2] that is, in part, responsible for paclitaxel's impressive ability to stabilise microtubules.[3] As a consequence, many analogues of paclitaxel possessing a modified side chain have been made by semi-synthesis.[4] Many different synthetic routes to the side-chain have been developed and reviewed recently.[5] β-Lactams constitute one of the most important type of side-chain precursor and can be made *via* the Staudinger reaction between an imine and a ketene. As part of an ongoing programme, we have been making novel cytotoxic agents *via* semi-synthesis from naturally occuring taxanes.[6] During this study we have developed a new stereocontrolled route to the paclitaxel β-lactam side-chain precursor using a chiral auxiliary that is cleaved oxidatively from the lactam nitrogen atom.



	R	3:4	Yield (%)
a	Me	60:40	60
b	Et	75:25	58
c	^{i}Pr	50:50	53

Scheme 1

The β-lactam **3a** has previously been made by the Staudinger reaction between the imine **1a** and the ketene derived *in situ* from acetoxyacetyl chloride **2** (**3a**:**4a**, 75:25, 74%).[7] However, the β-lactam was ring-opened in

*Email: N.Lawrence@umist.ac.uk; Fax: 161 200 7677

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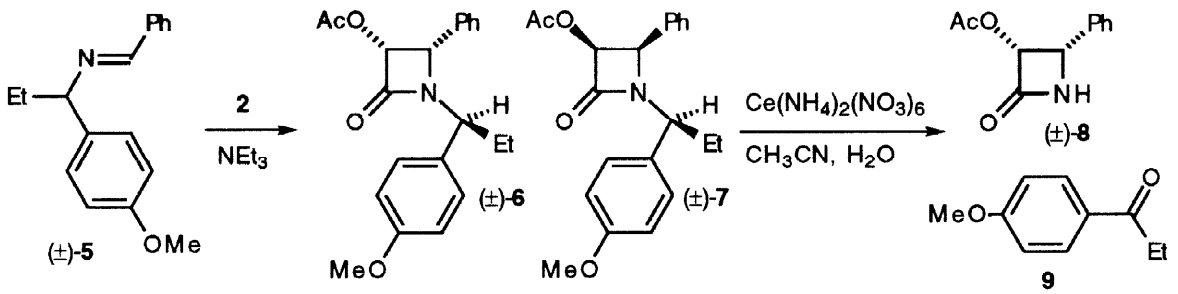
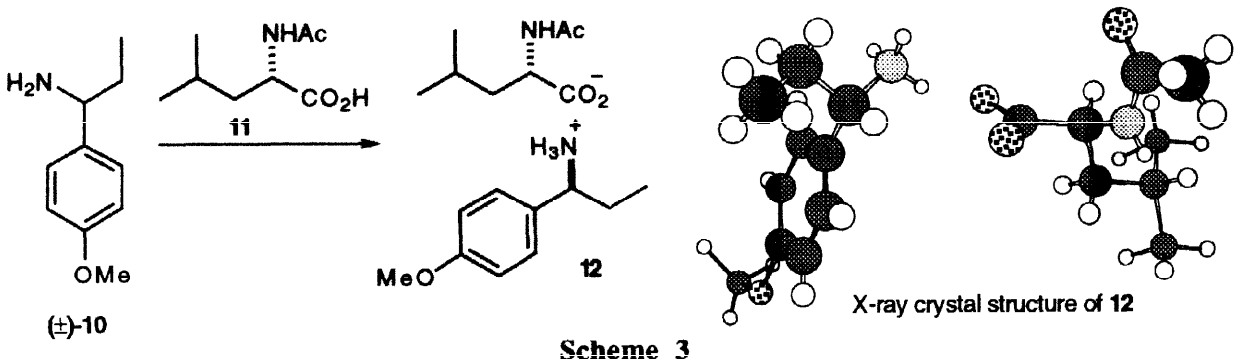
the next step of what constituted a synthesis of the phenylisoserine side-chain; the auxiliary was removed by hydrogenolysis. We wished to see whether the diastereoselectivity in the ring-forming reaction could be improved, and whether the auxiliary could be removed without destruction of the the β-lactam ring. The diastereoisomeric β-lactams (±)-**3a-c** and (±)-**4a-c** were prepared by the Staudinger reaction between the imines **1a-c** in the same way.[8] The size of the alkyl group present on the chiral centre clearly effects the degree of stereoselectivity of the reaction. Replacing the methyl group of **1a** with an ethyl group led to a significant increase in the desired diastereoisomer (±)-**3b**. However the imine **1c**, possessing an even larger alkyl group resulted in the formation of equal amounts of **4**(±)-**b** and (±)-**4c**. In all cases we were unable to observe the formation of the diastereoisomers possessing *trans* acetoxy and phenyl groups,within the limits of nmr detection. This is in agreement with the reported behaviour of so-called Bose-Evans ketenes.[9] Since it is known[10] that a *p*-methoxybenzyl group can be removed from a β-lactam with destruction of the β-lactam ring we prepared the diastereoisomers (±)-**6** and (±)-**7** in the usual way from the imine (±)-**5** (scheme 2). The stereoselectivity was only slightly lower than that obtained in the reaction of **1b** [(±)-**6**:(±)-**7** 67:33]. The selectivity was somewhat dependent upon the reaction solvent; in hexane, (±)-**6**:(±)-**7** 67:33, 54%; in benzene, (±)-**6**:(±)-**7** 74:26, 78%; and in DMF (±)-**6**:(±)-**7** 70:30, 85%. When the mixture of (±)-**6** and (±)-**7** was treated with ceric ammonium nitrate in a mixture of water and acetonitrile (3:5) for 1h at 0 °C the reaction proceeded cleanly to give the azetidinone (±)-**8** (85%) and *p*-methoxypropiophenone **9**. Whilst we do not have a convincing model to explan the origin of the diastereoselectivity in these Staudinger reactions, the sense of induction is the same as that of similar reactions employing other auxiliaries on the nitrogen atom.[11]



Scheme 2

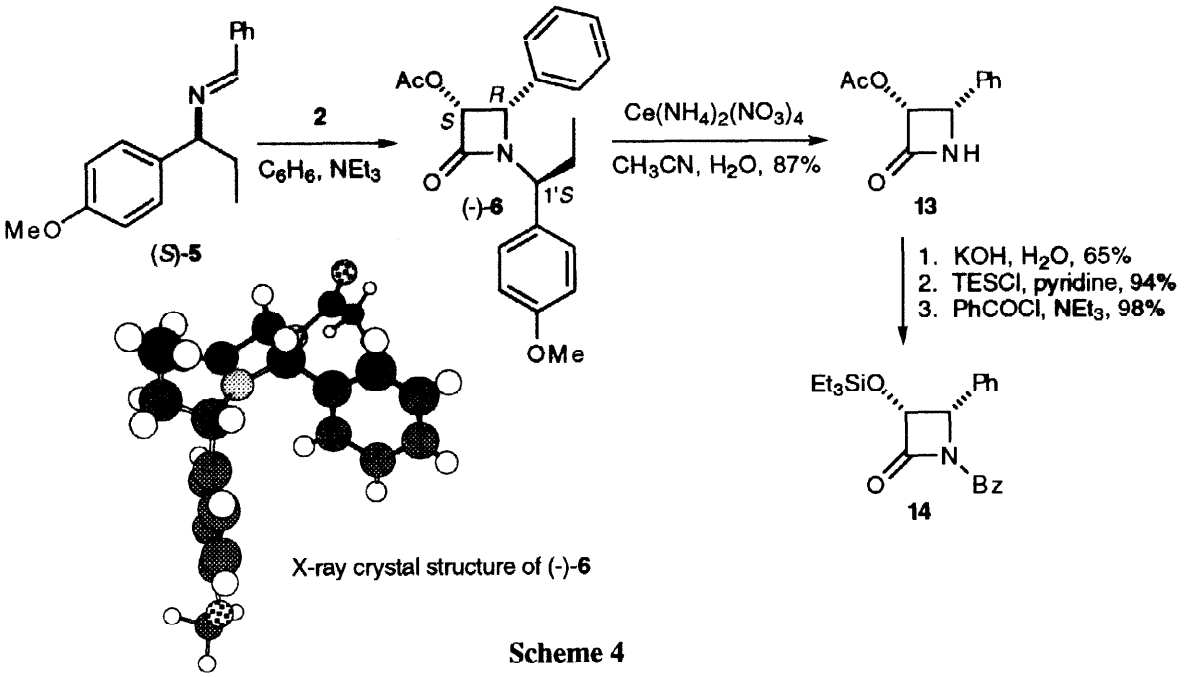
We prepared the enantiomerically pure (*S*)-(-)-1-(*p*-methoxyphenyl)propyl-1-amine (-)-**10** by resolution of its salt with *N*-acetyl-L-leucine **11**. The 1-(*p*-methoxyphenyl)propyl-1-amine (±)-**10** was in turn prepared in 89% overall yield by the sodium/ethanol[12] reduction of the oxime made from commercial (Lancaster Synthesis Ltd.) *p*-methoxypropiophenone **9**. Reaction of the amine with *N*-acetyl-L-leucine **11**[13] gave the diastereoisomeric salts. The (*S*)-amine *N*-acetyl-L-leucine salt **12** was obtained (30 %) by fractional crystallisation of the mixture from water. Treatment of the salt **12** with sodium hydroxide solution gave the amine (*S*)-(-)-1-(*p*-methoxyphenyl)propyl-1-amine[14] (quant.) and recovered *N*-acetyl-L-leucine **11** (88%), which had the same specific rotation as that of the starting sample. In this way we were able to rapidly prepare multi gramme quantities of (-)-**10** with e.e. >99% from the inexpensive starting materials *p*-methoxypropiophenone and L-leucine. The absolute configuration of the amine was confirmed as (*S*) by X-ray crystallography,[15] which clearly indicated that **12** was the (1*S*, 2'*S*) stereoisomer (scheme 3).

The imine (*S*)-**5** [quantitatively obtained from (*S*)-**10**] gave a 73:27 mixture (78%) of enantiomerically pure **6** and **7** upon reaction with acetoxyacetyl chloride. Fortunately the required major diastereoisomer (-)-**6** could be isolated free of **7** by recrystallisation from ethyl acetate/hexane (scheme 4)[52% from (*S*)-**5**].[16]



Scheme 3

X-ray crystal structure determination clearly showed that the isomer indeed possessed the required (1'*S*,3*S*,4*R*) configuration.[17] Treatment of the now pure (-)-**6** with with ceric ammonium nitrate gave the known azetidinone **13**.[18,19] We were able to isolate the by-product *p*-methoxypropiophenone **9** in 77% yield, which in principle can be recycled in the synthesis of further (*S*)-(-)-1-(*p*-methoxyphenyl)propyl-1-amine. Sequential deacetylation, silylation and benzoylation gave the known β-lactam **14** which has been successfully coupled to the C-13 side-chain of suitably protected 10-deacetyl baccatin III derivatives.



Scheme 4

In summary, we have show that the (*p*-methoxyphenyl)propyl-1-amine can be used as an auxiliary to control the diastereoselectivity in the Staudinger reaction between its imine derived from benzaldehyde and acetoxyacetyl chloride. The auxiliary can be oxidatively cleaved from the resultant β-lactam without destruction of the azetidinone ring, providing an efficient route to the paclitaxel side-chain.

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14 The enantiomers of the *N*-trifluoroacetyl derivative of **10** were clearly resolved by G.C. using a Chiraldex trifluoroacetyl-γ-cyclodextrin column.

15 *Crystal data* for **12**. $C_{18}H_{30}N_2O_4$: *M* 338.4, monoclinic, space group $P2_1$, *a* = 11.0097(10), *b* = 5.6856(10), *c* = 16.360(2) Å, α = 90°, β = 107.11(2)°, γ = 90°, *V* = 978.8.1(2) Å^3, Z = 2, D_C= 1.148 gcm^{-3}, T = 293 K, μ = 0.81 cm^{-1}. *Data collection and processing*: Full–matrix least–squares refinement using SHELXL93 yielded final residuals, based on F^2, of wR^2 = 0.1492 for all 1994 reflections and R_1 = 0.0398 for 1557 [I > 2σ(I)] reflections.

16 Selected data for (-)-**6**: rod-shaped crystals, m.p. 117-8 °C; Found C, 71.4 ; H, 6.7; N, 3.9. $C_{21}H_{23}NO_4$ requires C, 71.3; H, 6.6; N, 3.9%; $[\alpha]_D^{20}$ -11.8° (*c* 0.3, chloroform); δ ^{1}H (300 MHz, $CDCl_3$) 0.84 (3H, t, *J* 7.2 Hz, 3'-H), 1.66 (3H, s, Ac), 1.85 (2H, m, 2'-H), 3.80 (3H, s, OMe), 4.57 (1H, d, *J* 4.8 Hz, 3-H), 4.62 (1H, t, *J* 9.3 Hz, 1'-H), 5.62 (1H, d, *J* 4.8 Hz, 4-H), 6.83 (2H, d, *J* 8.2 Hz, 3"-H), 7.03 7.08 (2H, d, *J* 8.2 Hz, 2"-H), 7.27 (5 H, m, Ar); δ ^{13}C (75 MHz, $CDCl_3$) 7.7 (CH_3), 11.2 (CH), 26.5 (CH_2), 55.3 (CH_3), 59.3 (CH), 61.4 (CH), 76.2 (CH), 114.1 (CH), 128.0 (CH), 128.7 (CH), 128.8 (CH), 129.2 (CH), 129.7 (C), 134.0 (C), 159.2 (C), 164.9 (C), 169.1 (C); (CI: found: $[M + H]^+$ 354.1708. $C_{21}H_{23}NO_4$ requires 354.1705); *m/z* (FAB) 376 ($[M + Na]^+$, 10%), 354 ($[M + H]^+$, 50), 307 (20), 149 (100).

17 *Crystal data* for (-)-**6**. $C_{21}H_{23}NO_4$: *M* 354.4 monoclinic, space group $P2_1$, *a* = 12.133(2), *b* = 6.2723(10), *c* = 13.056(2) Å, α = 90°, β = 91.56(3)°, γ = 90°, *V* = 955.1(3) Å^3, Z = 2, D_C= 1.229 gcm^{-3}, T = 293 K, μ = 0.85 cm^{-1}. *Data collection and processing*: Full–matrix least–squares refinement using SHELXL93 yielded final residuals, based on F^2, of wR^2 = 0.0983 for all 1850 reflections and R_1 = 0.0388 for 1354 [I > 2σ(I)] reflections.

18 Selected data for azetidinone **13**; m.p. 151-52 °C (Lit.[19] 151-53 °C); $[\alpha]_D^{20}$ -45.7° (*c* 0.4, chloroform) {lit.[19] $[\alpha]_D^{20}$ -44.5° (*c* 1, chloroform)}.

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