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A Practical Access to Chiral Phenylisoserinates, Preparation of Taxotere® Analogs

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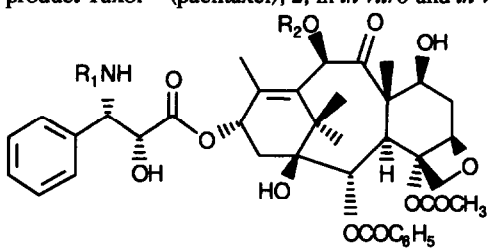
Abstract: A practical diastereoselective synthesis of phenylisoserine methyl esters **8a-c** is described using α-methyl-benzylamine as the chiral template of a Staudinger reaction. Optically pure diastereoisomers **6a-c** were easily recovered by crystallization. After opening of these intermediate azetidinones by hydrochloric acid and methanol, regioselective cleavage of the chiral auxiliary was achieved by hydrogenation over palladium. Phenylisoserinates **8b,c** were used to prepare analogs of Taxotere®.

Taxotere® (docetaxel), **1**, which is currently in phase II clinical trials, is a promising new anticancer agent and the first semisynthetic taxoid prepared so far that exhibits a higher level of activity than the related natural product Taxol® (paclitaxel), **2**, in *in vitro* and *in vivo* experimental models[1].



1, R_1 = tBuOCO, R_2 = H (docetaxel)
2, R_1 = C_6H_5CO, R_2 = Ac (paclitaxel)

In a previous paper[2], we reported an enantioselective access to the phenylisoserine chain of docetaxel along with an oxazolidine-type chain protection to prepare docetaxel and paclitaxel without epimerization.

New methodologies to prepare the docetaxel and paclitaxel side-chains have been published recently[3] including several promising ones that utilize β-lactams as intermediates. For instance Ojima and coll. have developed an elegant method for the preparation of (3R,4S) β-lactams in high optical purity using chiral enolate chemistry[4]. The product azetidinones are then N-acylated (introduction of a N-benzoyl or N-tert-butoxycarbonyl group) and opened by sodium or lithium baccatin alcoholates[5].

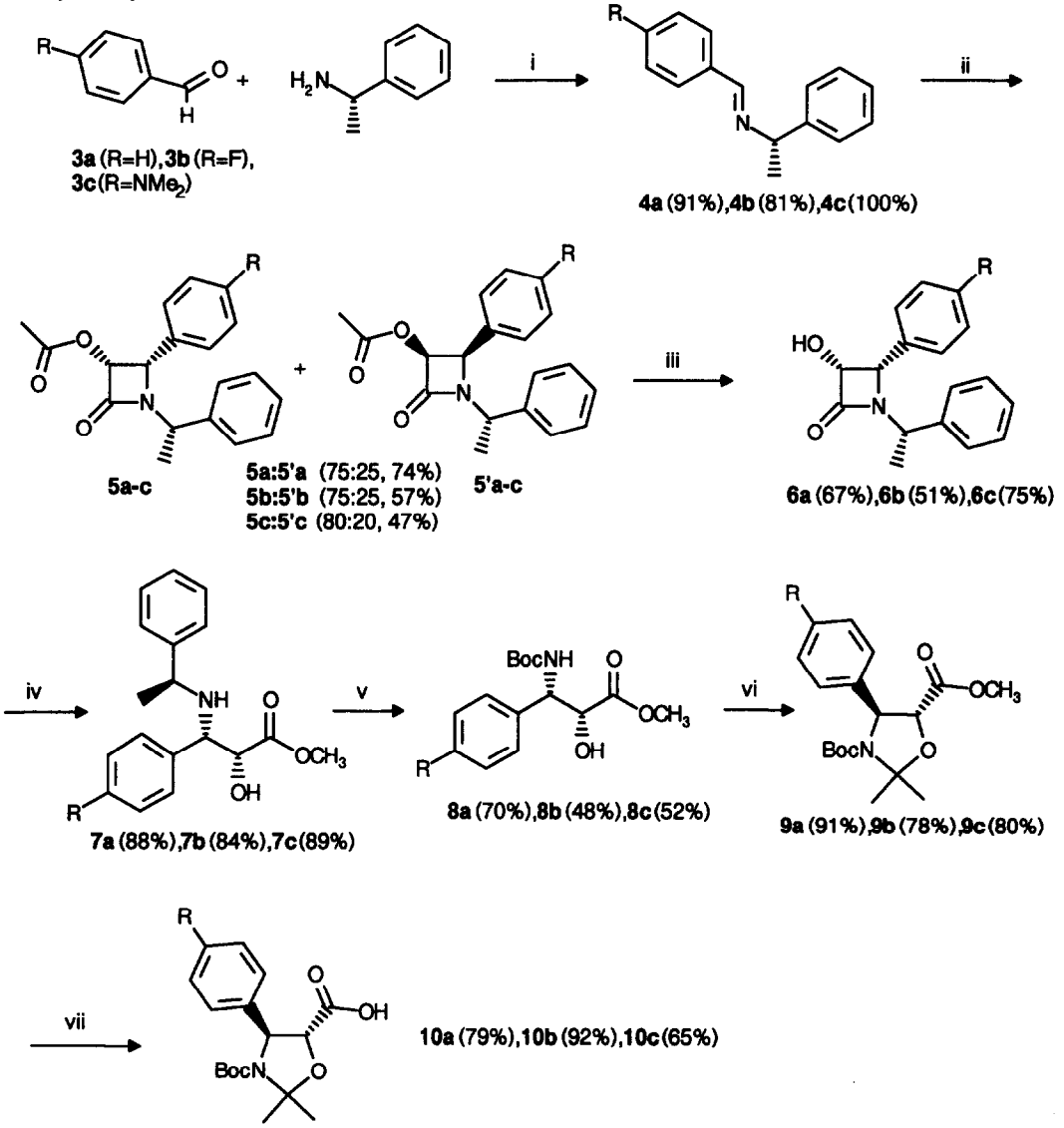
The ketene-imine cycloaddition process, frequently referred to as the Staudinger reaction, provides the most direct access to the β-lactam nucleus. Stereochemical control of this process has been proven possible employing chiral ketene or imine synthons[6].

Two different approaches to phenylisoserines have been published using the Staudinger reaction[7]. Georg and coll. used chiral imines derived from galactose to form enantiomerically enriched cis-β-lactams which can be transformed to the unnatural (2S,3R) enantiomer of the paclitaxel side chain[7a].

With the technical collaboration of M.F. Marzin, C. Souder, J.C. Massey and F. Bernard

More recently Farina and coll. reported[7b] a diastereoselective synthesis of (3R,4S)-3-hydroxy-4-phenyl-2-azetidinone using L-threonine as a chiral template[8]. The activity in this synthetic area has prompted us to disclose our results.

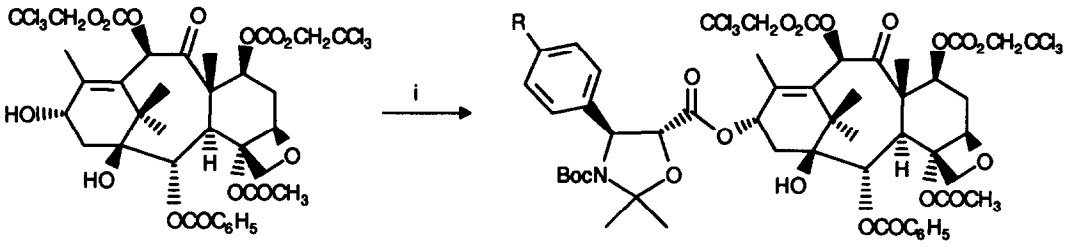
Our method was inspired by diastereoselective conditions recently published by Teutsch and coll.[9], who obtained 30-80% d.e. in the Staudinger reaction using imines formed from haloacetaldehydes and (R)-α -methyl-benzylamine.



Reagents: (i) CH_2Cl_2 , molecular sieves 4Å, 20°C, 70h. (ii) $AcOCH_2COCl$, $CHCl_3$, Et_3N, 0°C, 1.5h, then R.T. 3h. (iii) KOH/H_2O (1M), THF, 0°C, 1h, or NH_3, MeOH, 0°C, 1h, then crystallization from AcOEt. (iv) HCl (6N)/MeOH (5/1), reflux 20h, or HCl gas, MeOH, 40°C, 2.5h. (v) a) H_2 (345 psi), Pd/C (3%), MeOH/AcOH (3/1), 65°C, 4h, or H_2 (15 psi), $Pd(OH)_2$ (20%), MeOH/AcOH (20/1), 20°C, 18h. b) $(Boc)_2O$, CH_2Cl_2, Na_2CO_3, 20°C, 72h. vi) $CH_2=C(OCH_3)CH_3$ (8eq.), PPTS, toluene, 80°C (dist.). (vii) LiOH, EtOH, H_2O, 20°C, 2h, then H_3O^+.

Employing (S)-α-methyl-benzylamine as chiral template, imines **4a-c** were condensed with acetoxyacetyl chloride under standard conditions to give azetidinones **5a-c** and **5'a-c** (**5:5'** ratios varying from 75:25 to 80:20). Cleavage of the acetoxy group was easily achieved using ammonia or potassium hydroxide. From the crude mixture of diastereoisomers, optically pure **6a-c** were obtained by simple crystallization[10]. The lactams were then opened up by methanol in the presence of hydrogen chloride to yield the N-protected phenylisoserinates **7a-c**. The (S)-α-methyl-benzyl group proved to be more easily cleaved than the other benzylic moiety of the molecule upon hydrogenation in the presence of palladium[11] to give, after N-acylation, the N-Boc phenylisoserinates **8a-c**. Cyclic protection[2] using methoxypropene and a catalytic amount of pyridinium paratoluenesulfonate (PPTS) followed by saponification of the corresponding intermediates **9a-c** afforded acids **10a-c** in good yields.

Thus, the protected side chain equivalents **10a-c** may be obtained in few steps and with high optical purity (>99% by HPLC) from inexpensive starting materials. This approach has been proven general and useful to prepare other modified phenylisoserinates. Intermediates **10b** and **10c** have been used to synthesize the corresponding docetaxel analogs **1b,c** utilizing our previously described sequence[2].



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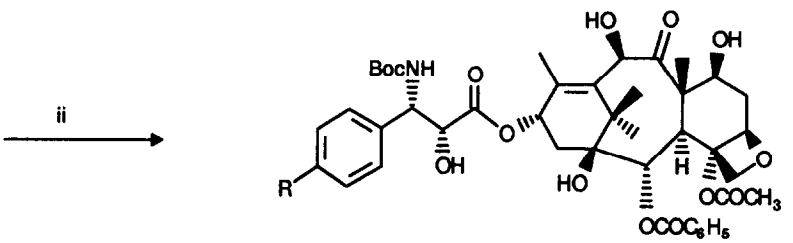

1b, R=F (23% overall yield)
1c, R=NMe_2 (42% overall yield)

Reagents: (i) **10b,c** (1.5eq.), DCC (1.6eq.), DMAP (0.5eq.), toluene, 80°C, 2h. (ii) a) HCOOH, 20°C, 4h., b) $(Boc)_2O$, CH_2Cl_2, $NaHCO_3$, 20°C, d) Zn, AcOH, MeOH, 60°C, 1h.

Esterification with O-diprotected baccatin III derivative **11**[12] gave esters **12b,c**. Deprotection under acidic conditions, N-acylation with $(Boc)_2O$ and reductive O-deprotection by zinc in acetic acid led to compounds **1b,c** in satisfactory yields.

Taxoid **1b** proved to be a very active docetaxel analog *in vitro* against P388 leukemia cells with an IC50 of 0.03 μg/ml (IC50 of docetaxel was 0.04μg/ml).

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References and notes:

1. For a recent review on preclinical studies on docetaxel, see: Lavelle F., Guéritte-Voegelein F., Guénard D., *Bull. Cancer*, **1993**, *80*, 326.
2. Commerçon A., Bézard D., Bernard F., Bourzat J.D., *Tetrahedron Lett.*, **1992**, *33*, 5185.
3. For very recent reviews about taxoid chemistry and the preparations of paclitaxel and docetaxel side chains see: Kingston D.G.I., Molinero A.A., Rimoldi J.M., *Fortsch. Chem. Organ. Naturstoffe*, **1993**, *61*, 1 and Nicolaou K.C., Dai W.M., Guy R.K., *Angew. Chem. Int. Ed. Engl.*, submitted.
4. Ojima I., Habus I., Zhao M., Georg G.I., Jayasinghe L.R., *J. Org. Chem.*, **1991**, *56*, 1681.
5. Ojima I., Habus I., Zhao M., Zucco M., Park Y.H., Sun C.M., Brigaud T., *Tetrahedron*, **1992**, *48*, 6985; Ojima I., Sun C.M., Zucco M., Park Y.H., Duclos O., Kuduk S., *Tetrahedron Lett.*, **1993**, *34*, 4149. Ojima I., Zucco M., Duclos O., Kuduk S.D., Sun C.M., Park Y.H., *Tetrahedron Lett.*, in press. We thank Professor I. Ojima for informing us of his results prior to publication.
6. Palomo C., Cossio F.P., Cuevas C., Lecea B., Mielgo A., Roman P., Luque A., Martinez-Ripoll M., *J. Am. Chem. Soc.*, **1992**, *114*, 9360; Borer B.C., Balogh D.W., *Tetrahedron Lett.*, **1991**, *32*, 1039; Evans D.A., Sjogren E.B., *Tetrahedron Lett.*, **1985**, *26*, 3783; Ojima I., Inaba S., *Tetrahedron Lett.*, **1980**, *21*, 2077; Kamiya T., Oku T., Nakaguchi O., Takeno H., Hashimoto M., *Tetrahedron Lett.*, **1978**, *51*, 5119; for a review, see: Labia R., Morin C., *J. Antibiotics*, **1984**, *37*, 1103; for other leading references regarding asymmetric versions of the Staudinger reaction see: Cooper R.D.G., Daugherty B.W., Boyd D.B., *Pure and Appl. Chem.*, **1987**, *59*, 485 and Kobayashi Y., Takemoto Y., Ito Y., Terashima S., *Tetrahedron Lett.*, **1990**, *31*, 3031; for asymmetric and mechanistic aspects, see also: Cossio F.P., Ugalde J.M., Lopez X., Lecea B., Palomo C., *J. Am. Chem. Soc.*, **1993**, *115*, 995; Sordo J.A., Gonzales J., Sordo T.L., *J. Am. Chem. Soc.*, **1992**, *114*, 6249; Hegedus L.S., Montgomery J., Narukawa Y., Snustad D.C., *J. Am. Chem. Soc.*, **1991**, *113*, 5784; Lynch J.E., Riseman S.M., Laswell W.L., Tschaen D.M., Volante R.P., Smith G.B., Shinkai I., *J. Org. Chem.*, **1989**, *54*, 3792.
7. a) Georg G.I., Mashava P.M., Akgün E., Milstead M.W., *Tetrahedron Lett.*, **1991**, *32*, 3151 and Corrigendum in *Tetrahedron Lett.*, **1992**, *33*, 1524; Georg G.I., Akgün E., Mashava P.M., Milstead M.W.,Ping H., Wu Z., Vander Velde V., *Tetrahedron Lett.*, **1992**, *33*, 2111. b) Farina V., Hauck S.I., Walker D.G., *Synlett*, **1992**, 761.
8. Tenneson S.M., Belleau B., *Can. J. Chem.*, **1980**, *58*, 1605.
9. Aszodi J., Bonnet A., Teutsch G., *Tetrahedron*, **1990**, *46*, 1579.
10. All new compounds exhibited IR, ^{1}H and ^{13}C-NMR spectra, mass spectral and combustion data in agreement with the structures indicated. As examples, we report herein the ^{1}H-NMR data of docetaxel precursors:
    6a: mp: 162°C, $[\alpha]_D^{20}$ +132 (C=1.08, MeOH), ^{1}H-NMR (200MHz; $CDCl_3$): δ 7.5-7.2 (m, 10H, Ph), 5.06 (q, 1H, J=7 Hz, C<u>H</u>CH3), 4.9 (dd, 1H, J=8.5 Hz, J=4.5 Hz, C<u>H</u>OH), 4.58 (d, 1H, C<u>H</u>Ph), 2.36 (d, 1H, OH), 1.41 (d, 3H, CHC<u>H</u>3).
    7a: oil, $[\alpha]_D^{20}$ -23 (C=1, MeOH), ^{1}H-NMR (200MHz; $CDCl_3$): δ 7.45-7.2 (m, 10H, Ph), 4.35 (d, 1H, J=4 Hz, C-3H), 4.2 (d, 1H, J=4 Hz, C-2H), 3.84 (s, 3H, COOC<u>H</u>3), 3,71 (q, 1H, J=7 Hz, PhC<u>H</u>MeNH), 2.7 (m, 2H, NH and OH), 1.34 (d, 3H, CHC<u>H</u>3).
    8a: mp: 135°C, $[\alpha]_D^{20}$ -7 (C=1, $CHCl_3$), ^{1}H-NMR (200MHz; $CDCl_3$): δ 7.45-7.2 (m, 5H, Ph), 5.3 (d, 1H, J=10.5 Hz, NH), 5.22 (br d, 1H, J=10.5 Hz, C-3H), 4.48 (m, 1H, C-2H), 3.87 (s, 3H, COOC<u>H</u>3), 3,16 (d, 1H, J=5 Hz, OH), 1.42 (s, 9H, tBu).
11. Furukawa M., Okawara T., Noguchi Y., Terawaki Y., *Chem. Pharm. Bull.*, **1979**, *27*, 2795.
12. Sénilh V., Guéritte F., Guénard D., Colin M., Potier P., *C. R. Séances Acad. Sci. Paris*, (série 2), **1984**, *299*, 1039.

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