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SYNTHESIS OF *TRANS*-1-*p*-METHOXYPHENYL-3-ACETOXY-4-PHENYLAZETIDIN-2-ONE. A KEY STARTING ß-LACTAM FOR 2'-EPI-TAXOL

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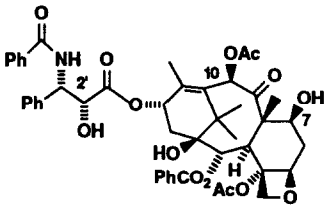
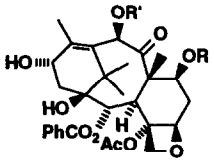
Abstract: *trans*-1-*p*-Methoxyphenyl-3-acetoxy-4-phenylazetidin-2-one (**9**) was obtained in high yield by changing the order of addition of the reagents in the acid chloride-imine cycloaddition of **5** and **6**.

Taxol® (**1**), a natural product of the Pacific yew,[1] is emerging as a useful anti-tumor drug with particular effectiveness against ovarian cancers.[2] The shortage of taxol® has spurred intensive research aimed at partial and total syntheses.[3] The semisynthesis disclosed by Holton[4] uses (+)-*cis*-β-lactam **3**, a precursor of the *N*-benzoyl-3-phenylisoserine sidechain of taxol®, to acylate the protected taxol nucleus (**2** R'=Ac, R=Et_3Si) which is derived from 10-deacetylbaccatin III (**2** R'=R=H)[5].



1 Taxol



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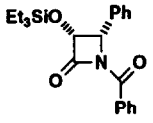

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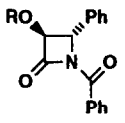

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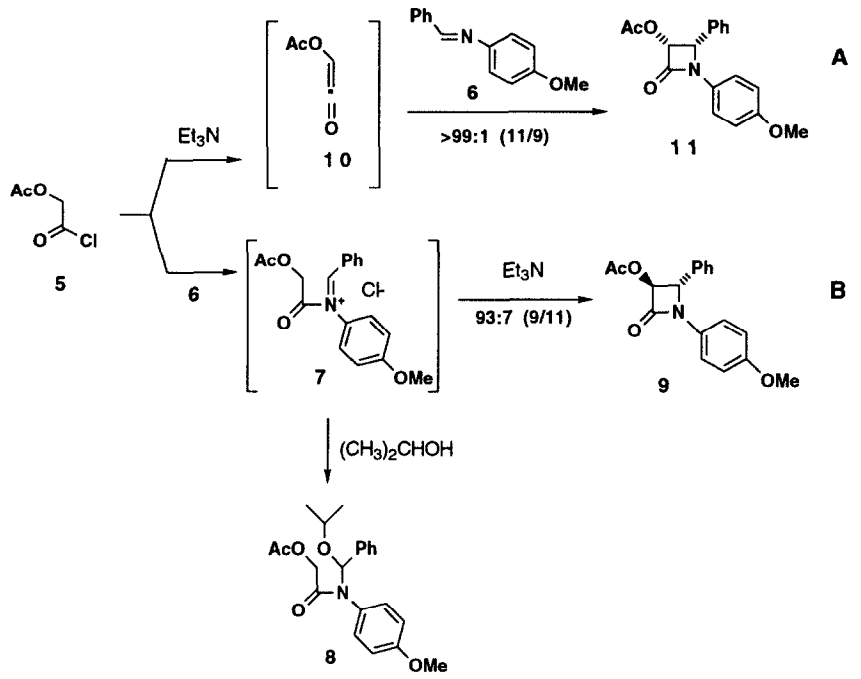
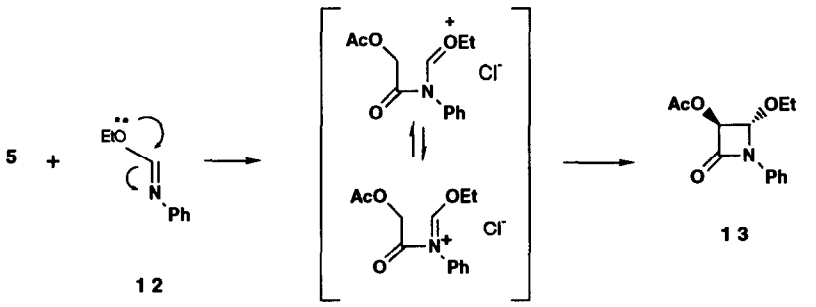
One of the goals of the ongoing process research in the Bristol-Myers Squibb laboratories was the preparation of 2'-epi-taxol for use as an analytical standard. To this end, the most expedient approach seemed to be the application of Holton's methodology[4] for the semi-synthesis of taxol® using *trans*-β-lactam **4**.[6] In this communication, we describe an efficient synthesis of **9**, the racemic precursor of β-lactam **4**.

It is well known that addition of acid chlorides to imines in the presence of base (Et_3N) results in *cis*-β-lactams, presumably through a process under kinetic control (Path A[7, 8]). Conversely, if an acid chloride is mixed with an imine in the absence of base, the acyliminium chloride **7** should form. When contacted with an external base, the iminium salt would be expected to give a *cis/trans* mixture or *trans* isomer only (Path B[7,9]). As an example, the nitrogen of ethyl *N*-phenylformimidate (**12**) is nucleophilic and is expected to form an iminium salt readily; cycloadditions involving **12** give the trans-β-lactam regardless of the addition order of the reagents.[10] This suggests that if the iminium salt could be formed, the *trans* product (indicating thermodynamic control) would be expected as the predominant form.[11]

Thus, addition of triethylamine to **7** resulted in a 93/7 ratio of *trans/cis* isomers. The pure *trans* isomer **9** was then obtained in 76% yield by crystallization of this mixture. Interestingly, the ratio of isomers was essentially the same whether the reaction was carried out at 23°C, 42°C, or 100°C, in either toluene or methylene chloride as the solvent.





Although the *cis/trans* ratio in the cycloaddition reaction is not disclosed in Holton's patent, our results showed a better than 99/1 *cis/trans* ratio which is affected by temperature and solvent. For example, a 99.7/0.3 *cis/trans* ratio was obtained with methylene chloride at 0°C, while toluene gave 97/3 at the same temperature. When acid chloride **5** was added to a mixture of imine **6** and triethylamine at temperatures higher than 0°C, stereoselectivity was lost (*cis/trans* ratios of 93/7 at 21°C, 74/26 at 40°C, and 23/77 at 60°C).

In an experiment designed to verify the formation of the iminium chloride, the product formed from **5** and **6** was trapped with isopropanol to give a stable crystalline material identified as isopropanol adduct **8**.[12]

Although reversal of the isomeric ratios has previously been observed in these cycloadditions, this is believed to be the first example where the stereochemical control is so dramatic as to permit the efficient preparation of both isomers in pure form.

EXPERIMENTAL

trans-1-*p*-Methoxyphenyl-3-acetoxy-4-phenylazetidin-2-one (**9**)

In a 2 L/3-necked flask fitted with a mechanical stirrer, a condenser with Dean-Stark trap and an argon gas inlet were placed benzaldehyde (52.3 mL, 0.515 mol, 3% excess), *p*-anisidine (61.5 g, 0.50 mol) and toluene (1350 mL). It was heated at reflux for 2 h while collecting water. The reaction mixture was cooled to room temperature and to this, acetoxyacetyl chloride (53.8 mL, 0.50 mol) was slowly added. The resulting mixture was brought to 100°C, then triethylamine (76.5 ml, 0.55 mol) was dropwise added over 60 min. It was stirred at 100-105°C for 1.5 h. The reaction mix was cooled to 40°C, washed with 0.5N HCl (500 mL) and warm water (40°, 500 mL), dried over anhydrous magnesium sulfate (HPLC[13] of the solution showed *cis/trans* ratio of 7/93), concentrated to a volume of 750 mL, and allowed to stand at room temperature for 3 h and at 0°C for 0.5 h. White needle crystals were collected by filtration, washed with cold toluene (-50°C, 200 mL) and dried *in vacuo*. Yield 119.5 g (76.8%); HPLC:*cis/trans* 0.06/99.94; mp 103-4°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.19 (s, 3H, CH_3CO_2), 3.74 (s, 3H, CH_3OAr), 4.91 (d, J=1.6 Hz, 1H, H-4), 5.38 (d, J=1.6 H, 1H, H-3), 6.78-7.38 (m, 9H, Ar); IR (nujol): 1740 cm^{-1} (CO); MS m/e: 312 $(M+H)^+$; Anal. calcd for $C_{18}H_{17}NO_4$ (311.335): C 69.44, H 5.50 N 4.50; found: C 69.59, H 5.46, N 4.47.

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10. Two reactions were carried out in toluene, one with base initially present, the other with base added only after the iminium salt was formed. The NMR spectra of both crude products showed no *cis* product. The *trans* compound **13** was isolated by chromatography (silica gel) in 10 and 42% yield respectively. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31 (t, J=7.0 Hz, 3H, $CH_2\underline{CH_3}$), 2.19 (s, 3H, $COCH_3$), 3.73-3.89 (m, 2H, $\underline{CH_2}CH_3$, 5.30 (d, J=0.5 Hz, 1H, H-4), 5.59 (d, J=0.5 Hz, 1H, H-3), 7.16-7.53 (m, 5H, Ph). IR (neat) : 1752, 1775 cm^{-1} (CO).
11. There are several reports that *trans* isomers were exclusively obtained with formimidates and thioimidates. For examples, see reference 9.
12. Yield 27.87 g (75.1%); mp 120-120.5°C; ^{1}H NMR (200 MHz, DMSO-d6) d: 1.20, 1.25 (2d, J=5.9 and 6.2 Hz, 6H, $CH(\underline{CH_3})_2$), 2.05 (s, 3H, CH_3CO_2), 3.68 (s, 3H, CH_3OAr), 4.03 (m, 1H, $\underline{CH}(CH_3)_2$), 4.26 (s, 2H, CH_2), 6.80 (broad s, 4H, Ar), 7.04 (s, 1H, $\underline{CH}Ph$), 7.12-7.25 (m, 5H, Ar); Anal. calcd. for $C_{21}H_{25}NO_5$ (371.41): C 67.91, H 6.78, N 3.77; found: C 68.16, H 6.73, N 3.83.
13. HPLC condition: column, Micro-Porasil; 30 cm x 3.9 mm; 10μ particle size, eluent; ethyl acetate/hexane 30/70; 42 bar; 1 mL/min.; isocratic; sample, 0.5 mg/mL; 40 μ, detector, UV (270 nm).