Enzymatic preparation of optically active precursors of CPI, the DNA alkylation subunit of the naturally occurring antitumour antibiotic CC-1065

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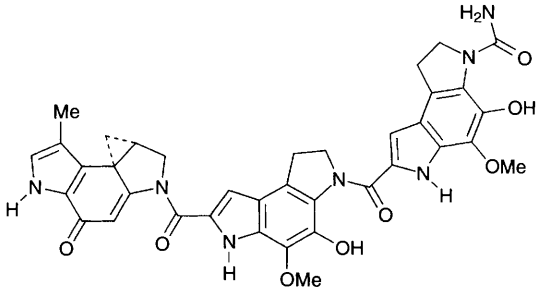
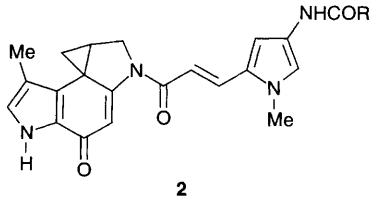
Some immediate precursors of CPI, the DNA alkylation subunit of CC-1065 are subjected to enzymatic resolution with Lipase PS in vinyl acetate; racemic 3 is effectively resolved by two consecutive enzymatic reactions.

CC-1065, an antitumour antibiotic isolated from the culture of *Streptomyces zelensis*,[1] is one of the most potent compounds discovered to date and has a wide spectrum of activities against tumour cells *in vitro* and *in vivo* as well as against microbial organisms.[2] CC-1065 binds to double-stranded DNA within the minor groove at AT-rich sites and alkylates the N-3 position of the 3′-adenine by its left hand subunit of cyclopropylindole (CPI).[3] Despite its high potency, CC-1065 cannot be used in humans because of the delayed death it causes in experimental animals. In the search for compounds with better antitumour selectivity, many CC-1065 analogues have been synthesized in attempts to avoid its unwanted side effects but to retain its potency against tumour cells.[4] In this regard, we have synthesized a series of analogues of CC-1065.[5] Among these compounds, a class of racemic analogues **2** has been found to have extremely high potency, even much higher than CC-1065.[5d]

With the chiral centre within the CPI unit, CC-1065 and other CPI bearing analogues are optically active compounds. The two enantiomers of these compounds showed different biological behaviour.[6] This prompted us to synthesize both enantiomers of **2**. It has been reported that the optically active precursors of CPI could be prepared by forming their diastereoisomers and separation of the latter by HPLC or crystallization.[4b,7] Some CPI related compounds were also obtained in a similar way or by separating the two enantiomers directly by chiral HPLC.[8,9] Because of the limitation of the quantity that can be treated by HPLC column and the troublesome process of forming diasteroisomers and crystallization, we have considered developing a more practical method, enzymatic resolution. Here we report our results.

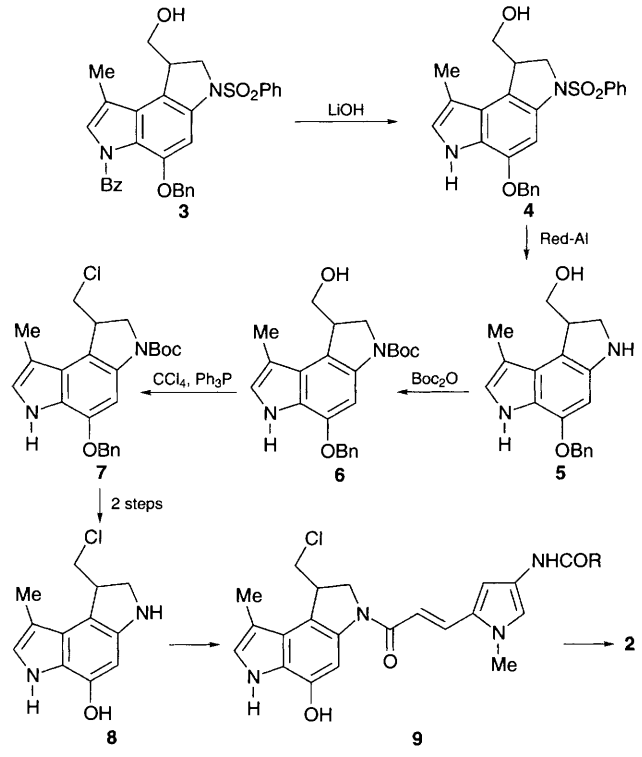


1 CC-1065



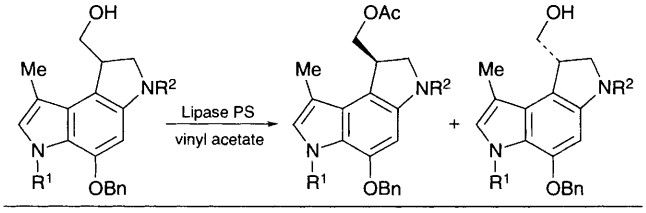
2

Lipase-catalysed *trans*-esterification is now widely used as an efficient and convenient method for resolution of hydroxy group containing compounds.[10] In the course of preparation of racemic **2** (Scheme 1),[4b,5] compounds **3**, **4** and **6** were considered to be suitable for resolution by this method. Therefore compounds **3**, **4** and **6** were subjected to enzymatic esterification in the presence of Lipase PS (Amano, lipase from *Pseudomonas sp.*) in vinyl acetate as solvent and acyl donor. The results are listed in Table 1. Lipase PS selectively acylated



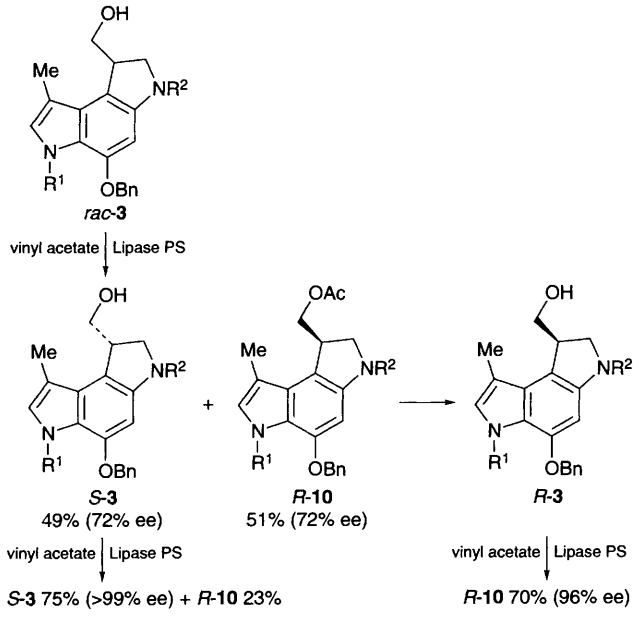
Scheme 1

Table 1



Substrate	Reaction time	Yield (%), (ee, %)	
3	72 h	41 (78)	53 (74)
4	2 weeks	44 (27)	54 (20)
6	68 h	43 (25)	46 (29)

the *R*-enantiomers of **3** and **6**. The absolute configuration of the products derived from **4** has not been determined. The best selectivity was observed with compound **3**. The acylated product was obtained in a yield of 41% with an optical purity of 78% ee. The remaining material was recovered in a yield of 53% with an optical purity of 74% ee. The optical purity of both products was enhanced by a subsequent kinetic resolution (Scheme 2).[11] The recovered natural enantiomer *S*-**3** was subjected to the same enzymatic reaction once more. The *S*-**3** was recovered from the second resolution in a yield of 75% with an optical purity of >99% ee. After the cleavage of the acetyl group of the unnatural enantiomer *R*-**10**, the resulting *R*-**3** was subjected to a second enzymatic reaction in the same way to afford *R*-**10** in a yield of 70% with an optical purity of 96% ee (Scheme 2). The optically pure *R*-**10** was obtained by quenching the reaction at lower yield (57%, >99% ee). It was found that the MTPA esters of racemic materials showed clearly two peaks (1 : 1) on ^{19}F NMR (400 MHz) spectrum. The chemical shifts of the MTPA ester of **3** was −71.93 and −72.08. So the optical purities of the products were determined by ^{19}F NMR after the products were transformed to their MTPA esters. The absolute configuration of the product was determined by transforming them to **6** and comparing the specific rotation value with the literature values.[4b,7]†



Scheme 2

We are grateful for the research grant (to J. W. L.) from the National Cancer Institute of Canada.

Footnote

† The specific rotation of compound **6** derived from optically pure *S*-**3** was $[\alpha]_D^{24}$ −10.5 (*c* 0.21, CH_2Cl_2); lit.,[4b] $[\alpha]_D^{23}$ −7.5 (*c* 0.74, CH_2Cl_2).

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