Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 915–918

TETRAHEDRON: *ASYMMETRY*

Stereoselective acylation of 20-(*S*)-camptothecin with amino acid derivatives using scandium triflate/DMAP

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Received 23 January 1998; accepted 29 January 1998

Abstract

Facile esterification of the hindered 3° alcohol 20-(*S*)-camptothecin with Boc protected chiral amino acids or derivatives under mild conditions has been achieved in high yield using the combination of $Sc(OTf)_3$ and DMAP. The isomeric purity of the product was maintained under these conditions.

In the course of our investigations[1] on the use of amino acid spacer groups with poly(ethlylene glycol) ester prodrugs of 20-(*S*)-camptothecin (an anti-cancer alkaloid displaying a highly hindered 3° OH functionality at the 20-position), we had occasion to prepare both diastereoisomeric esters derived from acylation of 20-(*S*)-camptothecin (**1**) with the Boc protected enantiomers of alanine (Ala). Esterification of the hindered 20-OH group was accomplished in over 90% yield by employing diisopropyl carbodiimide (DIPC) at 0°C in the presence of 4-dimethylaminopyridine (DMAP), but was accompanied by substantial epimerization for each stereoisomer: *t*-Boc-(*S*)-Ala (25%) and *t*-Boc-(*R*)-Ala (40%).[2] Rapoport and coworkers[3] devised a method that was reported to give high yields of *t*-butyl esters with little or no epimerization. However, this approach is not convenient since it entails the multi-step synthesis of a water soluble carbodiimide that must then be converted to a *t*-butyl isourea using cuprous chloride catalyst. Other recent advances in the acylation of 3° alcohols which produce high yields of esters employ symmetrical carboxylic acid anhydrides and the readily available Lewis acid catalyst, scandium triflate.[4] This procedure did not readily lend itself to the present goal since extension of the reaction to less available acids requires the use of mixed anhydrides, which in the case of 3° alcohols resulted in elimination. Thus, the synthesis of esters of 3° alcohols with diverse acids, especially amino acids, while maintaining configuration remains a challenging and difficult task.

We have now found that stereoselective esterification (conservation of isomeric purity) of 20-(*S*)-camptothecin is readily accomplished in high yield by a simple modification of the carbodiimide method. Thus, conducting the DIPC/DMAP process on acid **2** in the presence of $Sc(OTf)_3$ at low temperatures

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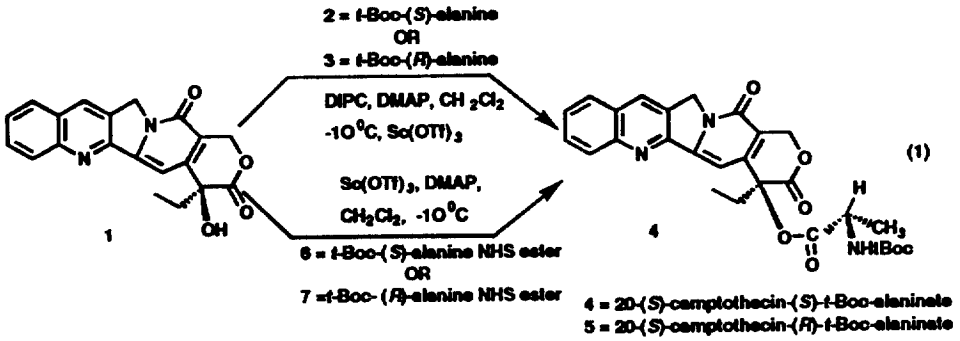
0957-4166/98/$19.00
PII: S0957-4166(98)00056-1

produced the desired 20-camptothecin ester **4** in 95% yield, which consisted of >97% pure diastereomer. Reactions appear to be complete in 3 h. Similarly, under these mild conditions **3** also provided compound **5** in high isomeric purity. The small amount of undesired diastereomer generated in these reactions can be removed by one crystallization with minimal effect on the overall yield. Further demonstration of the versatility of the $Sc(OTf)_3$–DMAP combination was provided by eliminating carbodiimide reagents and employing *N*-hydroxysuccinimide (NHS) esters **6** and **7** in place of the free acids. Using virtually the same reaction conditions, both **6** and **7** produced >98% stereoselective high yield esterification (Equation 1).



Since NHS esters are commercially available, or easily synthesized, this offers the additional choice of not having a condensing agent present during acylation. Table 1 provides a summary of the conditions and yields of esters obtained using the present method.

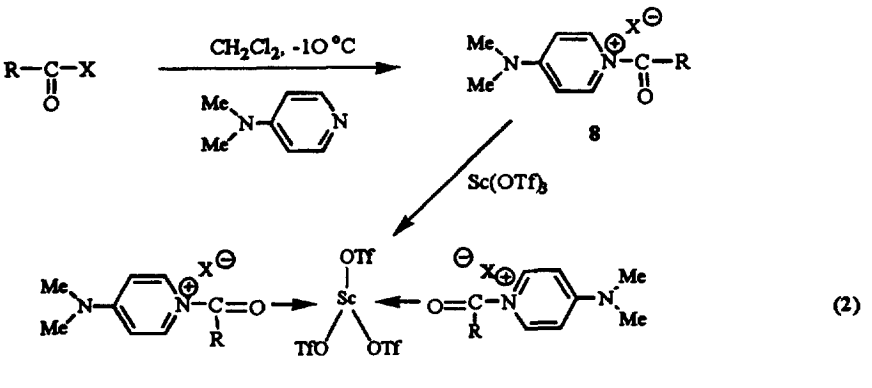
Table 1
Summary of acylations

3° Alcohol	Acid	Method[a]	Yield(%)[b]	ee (%) [c]
20-(*S*)-Camptothecin	*t*-Boc-(*S*)-(-)-Ala-OSu	B	94	99
20-(*S*)-Camptothecin	*t*-Boc-(*S*)-(-)-Alanine	A	95	99
20-(*S*)-Camptothecin	*t*-Boc-(*R*)-(+)-Ala-OSu	B	89	98
20-(*S*)-Camptothecin	*t*-Boc-(*R*)-(+)-Alanine	A	96	98
20-(*S*)-Camptothecin	(*S*)-(+)-2-Methyl butyric acid NHS ester	B	90	99

[a] Reference 8. [b] No attempts were made to optimize isolated yields in these cases. [c] Enantiomeric excess (ee %) was determined by HPLC analysis using either a chiral Phenomenex® Chirex column, or a C8 reverse phase column.

Experiments to determine reaction parameters and to help delineate the mechanism of this new procedure were initiated. No reaction of NHS ester **6** with **1** in the presence of DMAP alone was detected. Similarly, **6** and $Sc(OTf)_3$ alone did not catalyze the esterification of **1**, and only a small amount of product was observed after 24 h. Addition of triethylamine or the stronger base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), to this $Sc(OTf)_3$ reaction also did not produce the desired ester. When DBU and $Sc(OTf)_3$ were tried with **6** and *t*-butanol (a less hindered 3° alcohol), a slow reaction was initiated which appeared to be about 90% complete after 24 h at room temperature: however, DBU appeared to have caused complete equilibration of the ester product. This evidence strongly suggests that stereoselective acylation proceeds initially by formation of an acyl dialkylaminopyridinium intermediate (**8**).[5] Since this is a convergent process, it should not be dependent on any particular carboxylic acid derivative. This hypothesis is in agreement with utilizing $Sc(OTf)_3$ as an adjunct to the carbodiimide mediated reaction: nearly identical yields and chiral purity of diastereomer **4** resulted as those obtained

in the case of NHS ester **6**. Dative bonding of carbonyl oxygen to $Sc(OTf)_3$ during lactonization has been previously postulated.[6] Correspondingly, in these acylations the role of $Sc(OTf)_3$ may be to coordinate with the acyl pyridinium intermediate **8** to produce the highly reactive species, **9**[7] (Equation 2). Subsequently, acylation of alcohols by **9** would occur so rapidly that concomitant racemization of chiral intermediates is simply precluded.



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In summary, we have shown that addition of $Sc(OTf)_3$ to acyl pyridinium ion intermediates greatly facilitates reaction with hindered 3° alcohols as exemplified by camptothecin.[8] By accelerating acylation, reactions can be conducted at low temperatures and the chiral integrity of substrates preserved in those cases where DMAP would normally cause epimerization. We are currently exploring other combinations of 3° alcohols and carboxylic acids using this new methodology in order to demonstrate its generality. We anticipate presenting the results of this study shortly.

References

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2. Under similar conditions, the preparation of the less hindered *t*-butyl ester, *t*-butyl-L-Cbz-Ala using *t*-butanol and DCC, no racemization of the product was observed. Csanady, G.; Medzihradszky, K. *OPPI Briefs*. **1988**, *20*, 180–184.
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7. The coordination number of two has been designated arbitrarily.
8. *Method A.* Acylation of 20-(*S*)-camptothecin (**1**) with *t*-Boc-(*S*)-alanine (**2**) using DIPC/$Sc(OTf)_3$/DMAP: A suspension of **1** (0.1 g, 0.288 mmol), scandium triflate (Aldrich Chemical Company, 0.085 g, 0.173 mmol), **6** (0.163 g, 0.864 mmol), and DMAP (0.11 g, 0.864 mmol) in anhydrous methylene chloride (10 mL) was cooled to −8°C in an ice–salt bath for 30 min. DIPC (0.142 mL, 0.907 mmol) was added and the reaction mixture stirred at −8°C for 30 min and allowed to warm to room temperature over 2 h. The reaction mixture was filtered and the filtrate was washed with 20 mL of 0.1 N HCl, 20 mL of 0.1 M $NaHCO_3$, 20 mL of distilled water and then dried over anhydrous $MgSO_4$. Evaporation of the solvent left the crude product. Purification was accomplished by recrystallization from 10 mL of methanol to give pure (*S,S*)-camptothecin-20-*t*-Boc-alaninate (**4**) (0.140 g, 0.271 mmol, 94%). ^1H NMR (270 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.18–8.21 (m, 1H), 7.9–7.93 (m, 1H), 7.78–7.82 (m, 1H), 7.62–7.65 (m, 1H), 7.3 (s, 1H), 5.37–5.72 (AB q, 2H), 5.3 (s, 2H), 5.04 (s, 1H), 4.47 (m, 1H), 2.25 (m, 2H), 1.53 (s, 9H), 1.5 (s, 3H), 0.97 (t, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 171.89, 167.12, 157.34, 155.07, 152.33, 148.97, 146.41, 145.57, 130.97, 130.47, 129.79, 128.36, 128.10, 128.10, 127.92, 120.09, 96.20, 80.10, 67.06, 49.93, 49.43, 31.70, 28.41, 18.11, 7.56. *Method B.* Acylation of **1** with **6** using $Sc(OTf)_3$/DMAP: A suspension of **1** (0.5 g, 1.44 mmol), scandium triflate (0.425 g, 0.864 mmol), and DMAP (0.527 g, 4.32 mmol) in anhydrous methylene chloride (50 mL) was cooled to −8°C in an ice–salt bath, followed by the addition of *t*-Boc-(*S*)-alanine N-hydroxysuccinimide ester (**6**,

1.24 g, 4.32 mmol). The reaction mixture was stirred at −8°C for 30 min and allowed to warm to room temperature over 2 h. The reaction mixture was worked up as in method A to give a solid residue which was recrystallized from methanol (70 mL) to provide compound **4** (0.701 g, 94%).