Asymmetric Synthesis

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Efficient Synthesis and Resolution of Pyrrolizidines**

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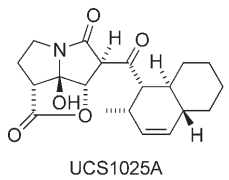
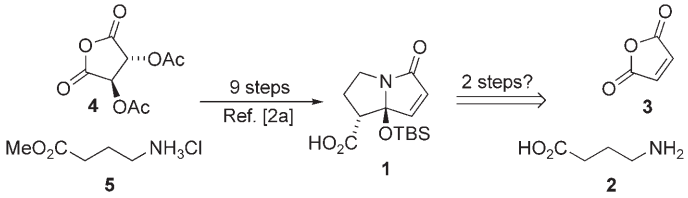
Dedicated to Professor Hans-Joachim Gais on the occasion of his 65th birthday

Azabicyclic alkaloids such as pyrrolizidines and indolizidines are a widespread class of biologically important natural products. We are particularly interested in the synthesis of the pyrrolizidine carboxylic acid unit integrated in the telomerase inhibitor UCS1025A.[1,2] In this communication, we will show that two unprecedented reactions involving free carboxylic acids allow for a two-step enantioselective synthesis of the pyrrolizidine fragment **1** of UCS1025A which compares quite favorably to Danishefsky's ex-chiral pool approach (**4**+**5**→**1**, Scheme 1).[2a]



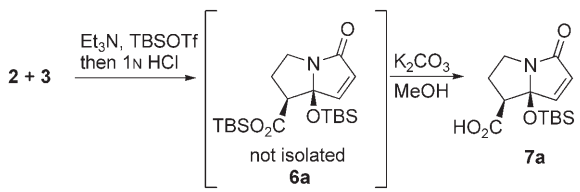
UCS1025A



Scheme 1. The ex-chiral pool approach to **1** and our synthetic strategy. TBS = *tert*-butyldimethylsilyl.

In the most efficient retrosynthesis of **1,** the pyrrolizidine could be assembled, in principle, in a single step from 4-aminobutyric acid (**2**) and maleic anhydride (**3**) as both compounds are in the required oxidation state (Scheme 1). A subsequent kinetic resolution would provide enantiopure material. However, such an approach would challenge some general assumptions concerning the activation of carboxylic acids. Firstly, it is commonly assumed that free carboxylic acids are poor precursors for the generation of active enolate equivalents. Secondly, despite the enantioselective addition of a plethora of nucleophiles to Michael acceptors,[3] an enantioselective addition of carboxylic acids has not been reported.

Inspired by the work of Rudler et al.[4] and Langer et al.[5] and in combination with the soft-enolization methodology developed by Hoye and co-workers,[2b,6] we speculated that bis-silylketene acetals formed in situ would provide an acceptable compromise between the reactivity and the desired lability of the ester products. This strategy sidesteps 4-maleimidoalkyl ester intermediates and the harsh basic conditions required for their hydrolysis. Toward this end, a solution of 4-aminobutyric acid and maleic anhydride was treated with triethylamine and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf; Scheme 2). Upon quenching



Scheme 2. Synthesis of the *cis* isomer **7a**.

with 1N HCl, the pyrrolizidine carboxylic acid silyl ester **6a** was obtained. Workup with potassium carbonate in methanol afforded the free carboxylic acid **7a**. We were surprised to see that the undesired *cis* diastereomer was formed with high selectivity. These results also suggest that the reaction does not proceed via a maleimide (vide infra).

When the commercially available maleimide **8** was submitted to the same conditions, the desired silylated *trans*-pyrrolizidine carboxylic acid **6b** was formed (Scheme 3). Depending on the workup, either tricyclic lactone **9** or the free carboxylic acid **7b** were obtained.

At this point, we wanted to test the scope and limitations of this reaction. With substituted maleimidobutyric acids, the reaction was shown to be completely regioselective and diastereoselective (Figure 1). Depending on the starting materials, either the *cis* (**10a**) or the *trans* products (**10b**, **10d**) were obtained. In analogy, 5-maleimidovaleric acid gave rise to the corresponding indolizidines (**10c**, **10f**). Finally, phthalimidobutyric acid gave the unsaturated tricyclic system (**10e**), which is a product from the elimination of TBSOH.

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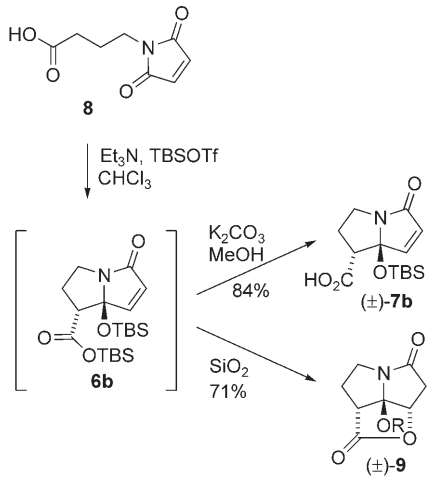


Scheme 3. Formation of the silyl ester **6b** and consecutive transformations into **7b** and **9** (R = TBS).

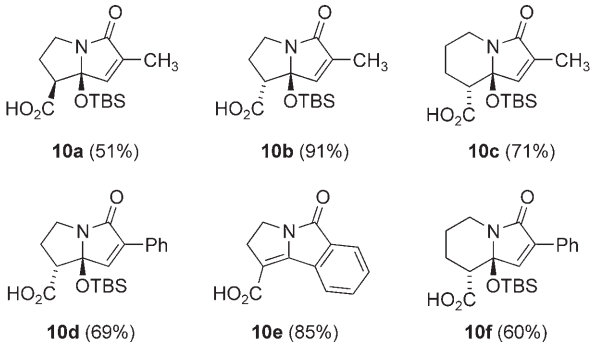


Figure 1. Substituted pyrrolizidines and indolizidines and yields of isolated products.

As **7b** is important as an intermediate in the synthesis of UCS1025A, we realized that a kinetic resolution of (±)-**7b** would be crucial for thorough biological investigations. Following the seminal work of Wynberg and Hiemstra,[7] many groups have studied the conjugate addition to Michael acceptors catalyzed by cinchona alkaloids. Of the nucleophiles employed, soft anions usually prevail, although progress has been reported in the intramolecular oxa-Michael addition of alcohols to α,β-unsaturated esters.[8] Interestingly, the enantioselective addition of a carboxylic acid to a Michael acceptor has not yet been achieved.

We dissolved (±)-**7b** and quinine (2:1) in CD_2Cl_2 and were fortunate to observe a kinetic resolution process in the NMR tube. In solution, quinine (like a shift reagent) and the enantiomers of **7b** form diastereomeric ion pairs, which lead to isolated resonances (H_a, H_b, and H_c) indicative of the reaction progress. As evident in the ^1H NMR spectrum in Figure 2, (−)-**7b** cyclizes considerably faster than its enantiomer to form the enantiomerically enriched lactone **9**. The enantiomeric ratio of the carboxylic acids and the conversion can be determined easily by integration of the respective resonances. It is important to note that this system may contribute to the understanding of cinchona-alkaloid-catalyzed processes, since solvent effects, catalyst performance, and kinetics are directly observable.

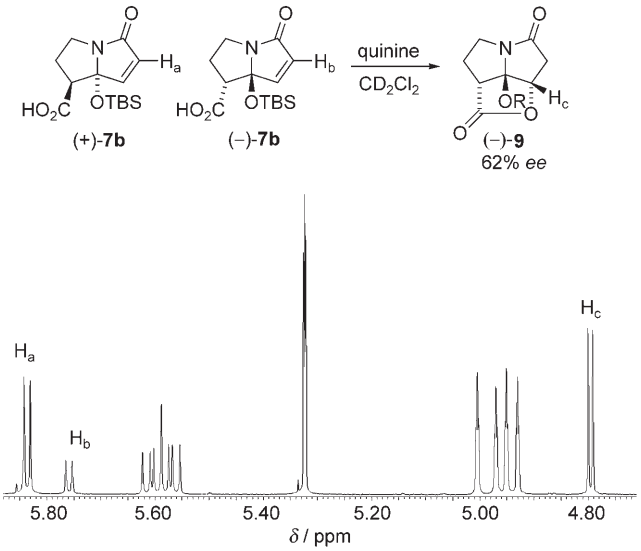


Figure 2. Enantioselective lactonization.

Table 1 summarizes a screening of cinchona alkaloids in some common NMR solvents. The catalyst and solvent have a pronounced effect on the reaction rate and the selectivity. We found that at ambient temperature dichloromethane is superior to chloroform and benzene, and that quinine is the base of choice. High selectivity can be achieved, although the reaction slows down significantly at 4 °C (entry 8, Table 1). If (−)-**7b** is the desired enantiomer, quinidine can be employed or alternatively (−)-**9** was easily converted back to (−)-**7b** by β-elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Table 1: Catalyst and solvent screening for the formation of lactone (−)-**9** from (±)-**7b**.[a]

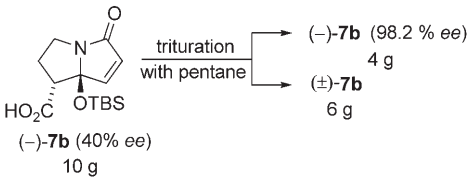
Entry	Solv.	Amine base	*T* [°C]	*t* [d]	(+)-**7b** [%]	(−)-**7b** [%]	(−)-**9** [%]
1	$CDCl_3$	quinine	25	1	43	24	33
2	$CDCl_3$	hydroquinine	25	1	44	25	30
3	$CDCl_3$	cinchonine	25	1	41	35	24
4	CD_2Cl_2	quinine	25	1	40	13	47
5	C_6D_6	hydroquinine	25	1	35	16	49
6	CD_2Cl_2	quinidine	25	1	33	44	23
7	CD_2Cl_2	cinchonidine	25	1	33	39	28
8	CD_2Cl_2	quinine	4	7	50	29	21[b]

[a] Reaction conditions: 1 equiv (±)-**7b**, 0.5 equiv amine base. The ratios were determined by ^1H NMR spectroscopy. [b] By HPLC (−)-**9** was determined to have 62% *ee*.

Recently, Blackmond et al.[9] and Hayashi et al.[10] investigated the solid–liquid equilibrium of scalemic amino acids in different solvents and the effects on catalysis. The most striking example, serine, has its eutectic at > 99% *ee*.[11] It has also been known that trituration can influence the enantiomeric and diastereomeric composition of scalemic and diastereomeric mixtures.[12] Typically trituration is used to

remove minor impurities,[13] as in our case where we were just aiming separate lactone **9** from the carboxylic acid **7b**. Interestingly, we found that when a weakly enriched scalemic mixture of **7b** is triturated in hot *n*-pentane, (−)-**7b** is readily dissolved, while racemic **7b** remains as a solid residue (Scheme 4).

The spatial arrangement of homochiral or heterochiral molecules bearing donor and acceptor sites naturally leads to different



Scheme 4. Trituration enrichment at a high eutectic *ee*.

packing arrangements and solubility properties. As it can be seen in X-ray crystal structures of (±)-**7b** and (−)-**7b** (Figure 3), a strong intermolecular hydrogen bond between the carboxylic acid and the imide carbonyl group is the dominant motif. At this point it is difficult to argue why the

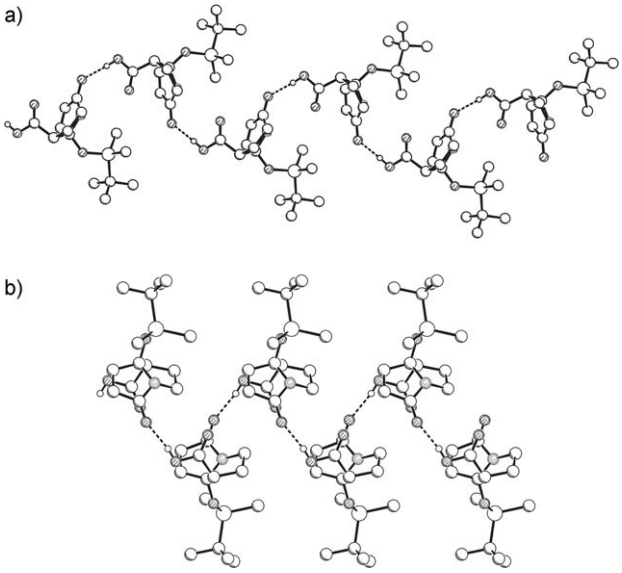
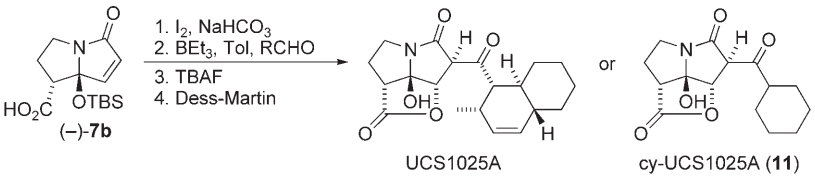


Figure 3. X-ray structures of a) (±)-**7b** and b) (−)-**7b**.

assembly of homochiral molecules leads to less favorable interactions.[14]

Using the elegant endgame strategy developed by Danishefsky et al.,[2a] we converted (−)-**7b** into UCS1025A and its cyclohexyl analogue **11** in just four further steps (Scheme 5). This opens the door for rapid generation of analogues, which should help in outlining structure–activity relationships for this important telomerase inhibitor.



Scheme 5. Danishefsky's coupling protocol for the synthesis of UCS1025A and cy-UCS1025A (**11**) from (−)-**7b**. TBAF = tetrabutylammonium fluoride. Tol = toluene.

We would like to underscore the point that four recent developments in reaction methodology now allow for a very efficient access to UCS1025A. Namely Hoye's soft-enolization cyclization,[2b,6] our oxa-Michael lactonization/trituration, MacMillan's organocatalytic Diels–Alder reaction,[15] and Danishefsky's BEt_3-mediated coupling[2a] have made UCS1025A available in gram scale for biological studies.

Further research from our laboratories will focus on the synthesis and evaluation of simplified analogues, extension of the oxa-Michael lactonization methodology, and an investigation of the structural requirements for high enantioselectivities at the eutectic point.

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[11] The practical consequence is that a nearly racemic sample can provide a nearly enantiopure solution in the solid–liquid equilibrium.
[12] One of the referees pointed out that recrystallization in which the solution has enriched *ee* is common for organic compounds (e.g. J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates and Resolutions*, Wiley, New York, **1981**, pp. 192–196). We would like distinguish the trituration from a crystallization process, where the solid is temporarily completely dissolved. In our case, a virtually quantitative separation of racemate is achieved in an operationally simple protocol. If the prerequisite of a high eutectic *ee* is fulfilled, this underutilized technique appears superior to classical recrystallizations.
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