Combining incompatible processes for deracemization of a Praziquantel derivative under flow conditions

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Abstract: *An efficient deracemization method for conversion of the racemate to the desirable (R)-enantiomer of Praziquantel has been developed by coupling incompatible racemization and crystallization processes. By a library approach a derivative that crystallizes as a conglomerate has been identified. Racemization occurs via reversible hydrogenation over a palladium on carbon (Pd/C) packed column at 130 °C, whereas deracemization is achieved by alternating crystal growth/dissolution steps with temperature cycling between 5-15 °C. These incompatible processes are combined by means of a flow system resulting in complete deracemization of the solid phase to the desired (R)-enantiomer (98% ee). Such an unprecedented deracemization by a decoupled crystallization/racemization approach can readily be turned into a practical process, and opens new opportunities for the development of essential enantiomerically pure building blocks that require harsh methods for racemization.*

Around 200 million people suffer from schistosomiasis (Bilharzia or snail fever), an infection caused by blood flukes.[1] Praziquantel (Biltricide) **1** (Figure 1) is used as racemate almost exclusively for treatment. The drug affects the permeability of membranes of the parasite towards calcium ions. The (*R*)-enantiomer is responsible for the pharmacological effect and tastes significantly less bitter than the cheaper racemate.[2]. Large and, especially for children, difficult to swallow bitter tablets of racemic **1** are currently used to obtain the desired therapeutic effect.

Pure enantiomers of Praziquantel can be obtained via classical resolution of precursor Praziquanamine **2** (Scheme 1) or its N-benzoyl derivative.[2a, 3] Praziquantel has been resolved by diastereomeric co-crystal formation with L-malic acid.[4] Recently, **1** has been resolved on semipreparative scale using simulated moving bed chiral chromatography.[5] These resolution procedures are all limited to a maximum yield of 50%. An efficient method to convert the racemate to enantiomerically pure (*R*)-Praziquantel is of obvious interest.

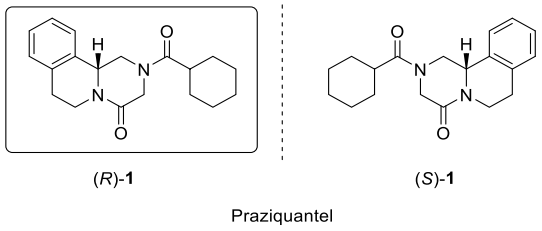


Figure 1. Racemic praziquantel **1** ((*R*)-**1**: (*S*)-**1** = 1 : 1) is used for treatment of Bilharzia whereas the active enantiomer is (*R*)-**1**.

Attrition enhanced deracemization (Viedma ripening)[6] and related temperature cycling techniques[7] are effective practical methodologies for total conversion of a racemate into the pure enantiomer in the solid phase (Figure 2). There are prerequisites: a) the compound must crystallize as a conglomerate;[8] b) a suitable method for liquid phase *racemization* is required for total *deracemization*, and c) the racemization conditions must be compatible with the crystallization conditions required for deracemization.[9]

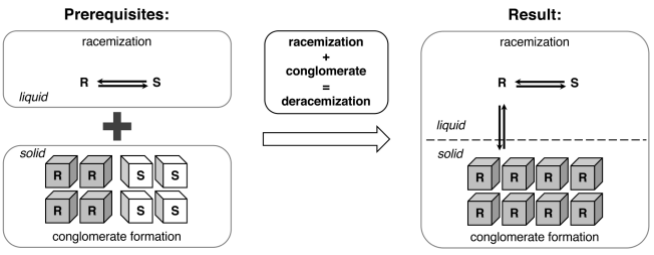
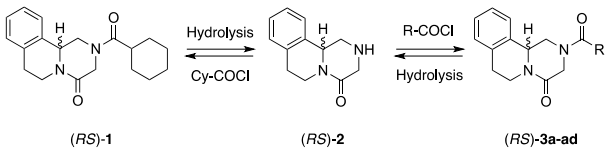


Figure 2. The prerequisites for deracemization.

Unfortunately, Praziquantel is not a conglomerate (prerequisite a); it crystallizes as a stable racemic compound.[10] However, this prerequisite can be met by synthesis and search of a covalent library of crystalline derivatives.[11] We prepared a library of 30 crystalline derivatives **3a-ad** obtained by reaction of **2** with acyl

and aryl chlorides (Scheme 1, Figure S1 SI). Derivatives **3** may be hydrolyzed and converted back to **1** (Scheme 1).[2a]



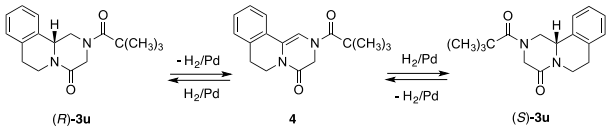
Scheme 1. Reversible derivatization of **2** for generating a library of compounds **3** as candidates for conglomerate screening. (Scheme 1, Figure S1 SI).

Second harmonic generation (SHG) was used for preliminary conglomerate screening.[12] Four compounds with positive responses were identified of which only the pivaloyl derivative **3u** proved to be a conglomerate (SI). This assignment was confirmed by Differential Scanning Calorimetry (DSC) measurements, X-ray powder diffraction (XRPD) and by crystal structure determination of a single crystal: orthorhombic non-centrosymmetric $P2_12_12_1$ space group (SI).

Prerequisite b: racemization methods for **1** and related structures are limited and require harsh conditions.[3, 13] Treatment with potassium tert-butoxide (t-BuOK) has been reported to racemize Praziquantel (**1**) and Praziquanamine (**2**). The reaction must be run at -15 °C in an apolar solvent under anhydrous conditions.[13b] A one-pot racemization of precursor **2** has been reported at 130 °C with palladium supported on carbon under H_2 atmosphere.[3, 13a] Long reaction times (48 hours) as well as high temperature and pressures are necessary.

Prerequisite c: compatibility of prerequisites a and b, requires that both crystallization and racemization occur simultaneously. The reported racemization conditions are incompatible with a crystallization process required for deracemization of **3u**. Nevertheless, reversible dehydrogenation-hydrogenation racemization remains an attractive approach if it can be separated from the crystallization.[13a] The reactivity of the hydrogen bound to the stereogenic center in **1, 2** and **3u** is increased by the adjacent aryl group.[3, 13f, 14] We found that compound **1** could be racemized cleanly in a flow system over a packed bed reactor filled with Pd supported on carbon, previously activated with H_2 at 130 °C, with just 2 minutes of residence time in the packed bed reactor (SI). Similar conditions were applied to **3u**. Racemization again proceeded cleanly (SI).

Trace amounts of the putative achiral dehydro- intermediate **4** were observed during reaction (Scheme 2, SI). Intermediate **4** was isolated and identified. No other side products were detected.



Scheme 2. Liquid phase racemization in a loop through a flow system.

The incompatibility issue was resolved with the decoupled flow system shown schematically in Figure 3. The crystal growth/dissolution process occurs in the crystallization unit, a thermostated reactor, and the mother liquor is continuously pumped to the racemization unit and racemized at 130 °C in a closed system. A filter was connected upstream to the pump and submerged into the slurry in order to deliver the mother liquor free of solids to the racemization unit. In order to drive deracemization in the direction of the desired enantiomer, (*R*)-**3u**, a small initial excess of the desired (*R*)-enantiomer must be present in the initial solid phase.

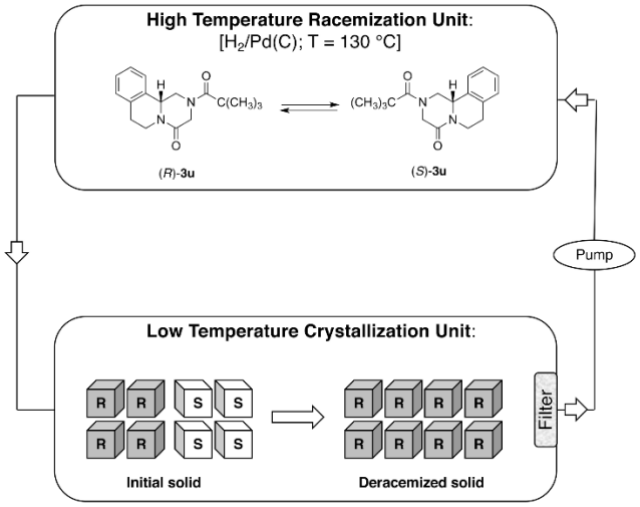


Figure 3. Schematic illustration of the decoupled system for deracemization.

Attrition enhanced deracemization (Viedma ripening) was first attempted to promote deracemization.[6c, 15] Unfortunately, this was unsuccessful owing to the slow growth rate relative to the rate of attrition that led to formation of extremely small and difficult to filter crystals. These crossed the filter submerged into the slurry, leading to a rise in pressure and clogging.

Alternatives to the attrition involved in Viedma ripening are crystallization induced asymmetric transformation (CIAT)[16] and temperature cycling-induced deracemization (TCID).[7a, 7d] Forced attrition is no longer necessary and, as a result, larger crystals form.

Toluene was first checked as solvent in a single step crystallization induced asymmetric transformation (CIAT) process. Roughly 10% seed crystals of the (*R*)-enantiomer, compared to the total amount of racemic **3u,** were added to the saturated solution, and the crystallization temperature was decreased from 15 to 5 °C over a 3 h period. In two CIAT experiments (*R*)-**3u** in approximately 90% ee was harvested in 12% and 32% yields, respectively, corrected for the seed mass used (entries 1 and 2, Table 1). However, from the complete material balance in Table 1 it is clear that in entry 1 little, if any, deracemization occurred. For entry 2, for which the ratio between the total volume of the system and the dead volume of packed bed reactor (total volume/dead volume ratio) was decreased (SI) significant deracemization did occur. However, for both entries 1 and 2 the mother liquors remained enriched in (*S*)-enantiomer (Table 1), probably owing to over-hydrogenation of the catalyst, which slowed the racemization rate.

TCID mode is advantageous because multiple cycles may be carried out with a single filtration in the end. Owing to solubility considerations the solvent was changed to methanol (MeOH, Figure S25, SI). Re-activation of the column was performed at the start of every cooling ramp of each temperature cycle by

delivering hydrogen. After initial experimentation we found that if short and frequent re-activation of the catalyst was not carried out, the TCID stopped (Figure S9, SI), probably because of lack of racemization in solution. Virtually complete conversion of the solid phase to the (*R*)-enantiomer was achieved after 10 cycles in about 18 h (Figure 4). The mother liquors were now racemic and solid (*R*)-**3u** harvest was obtained in 98% ee. The recovery of crystalline (*R*)-**3u** corrected for seed is 32% and the total amount of (*R*) has increased by 31-32% (Table 1, entry 3). The temperature cycling protocol closely resembles recently published guidelines.[17] Deracemization occurs thus readily and recharging with the mother liquor and fresh enriched (*R*)-solid would allow continuity. From the results of entry 3 and 4 it is clear that the process is reproducible. Recovered deracemized **3u** contained < 0.1 mg Pd per 1000 mg consistent with the absence of significant leaching from the catalyst.

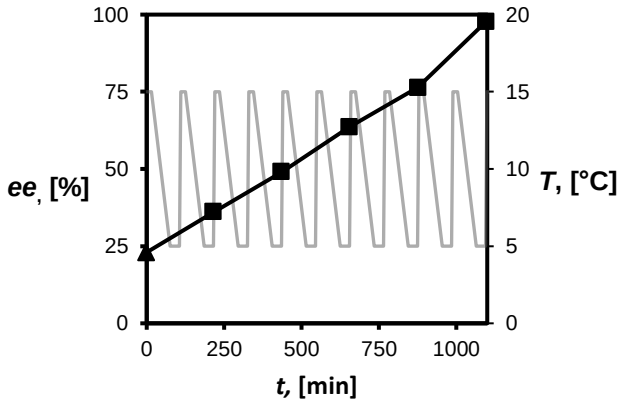


Figure 4. Evolution of the solid phase *ee* in (*R*)-**3u** at the end of cooling ramps as function of time. The gray segment represents the variation of temperature as function of time. Triangle represents the sample withdrawn at 5 °C, squares represent samples withdrawn at 5 °C.

Table 1. Results from the deracemization experiments.[18]

Exp	Starting conditions	Filtrate[a]		Isolated solid		Enrichment[e]
	Overall ee % (*R*)	Remaining in solution %	ee % (*S*)	Yield %[b]	ee % (*R*)	%
1[c]	8.9	79	11	21 (12)	89	+2
2[c]	7.3	61	6	39 (32)	92	+24
3[d]	9.6	58	0	42 (32)	97	+31
4[d]	10.0	57	0	43 (32)	98	+32

[a] Corrected for sampling. [b] In parenthesis yield corrected for initially added (*R*)-seed crystals. [c] Solvent: toluene, CIAT procedure. [d] Solvent: MeOH, TCID procedure. [e] Overall enrichment in (*R*)-enantiomer based on starting racemate.

Enantiomerically pure (*R*)-**3u** was hydrolyzed in 92% yield to the amine (*R*)-**2** in a mixture of ethanol/aq HCl (1N) overnight. The product was shown to be enantiomerically pure (SI) and was acylated in near quantitative yield with cyclohexanecarbonyl chloride to provide enantiomerically pure (*R*)-Praziquantel as previously described.[2a]

Modern crystallization induced deracemization methods offer a simple and efficient method to obtain chiral building blocks of extremely high enantiomeric purity in virtually quantitative yield.[19] Most of these deracemization methods using conglomerate-based technologies are restricted to cases where racemization and crystallization occur under mutually compatible conditions in a single reactor. Recently reported two-flasks combination of preferential crystallization with “ex-situ” racemization enabled deracemization of a drug precursor Mefloquine.[20] Racemization methods compatible with crystallization have remained limited: base-catalyzed racemization remains the most commonly used for deracemization,[11b-d, 21] although application of photo-chemically and redox induced variants have been reported.[22] Consequently, the essential requirement to combine racemization and conglomerate crystallization under mutually compatible conditions has greatly limited the application potential.

Our flow system approach opens up exciting opportunities for coupling crystallizations with other hitherto incompatible racemization reactions to develop new deracemization methods that were previously impossible.

Acknowledgements

Merck KGaA provided racemic and enantiopure **1** and **2** and Dr David Maillard (Merck) is thanked for advices. We are grateful to Prof Wesley Browne (Univ. Groningen) and Kees van der Loo (Syncom) for fruitful discussions and aid.

Deposition numbers 1997311-1997314 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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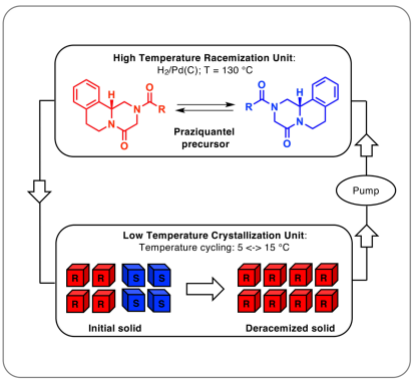

DRUGS "R" US.

The (R) enantiomer of Praziquantel is more active against Schistosomiasis (Bilharzia, snail fever). The cheaper, commonly used, racemate can be deracemized via a conglomerate derivative to this enantiomer, which is obtained in 98% ee using a flow system in which Pd catalyzed high temperature racemization is coupled to low temperature cycled crystallization. Broad applicability of this deracemization approach should be possible.