Synthesis of Enantioenriched 4-Thiazolidinone (-)-LY213829 by Chemoselective Benzylamide Cleavage in the Presence of a C-S Bond

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Abstract: (*R*)-2-Methylbenzylamine has been used to covalently "resolve" thiol acid **7** and assemble 4-thiazolidinone **8a** in one step. Selective deprotection of the 2-methylbenzylamide using lithium in ammonia/THF has been achieved in the presence of a readily hydrogenolyzed C-S bond. Enantioenriched (-)-LY213829 (**1**) of 98% ee has been prepared by this five step route in 25% yield from aldehyde **2**. Copyright © 1996 Elsevier Science Ltd

LY213829 (**1**) is under development for the treatment of inflammatory bowel disease. While proceeding with evaluation of racemic **1**, quantities of each enantiomer were required for comparative biological testing. A novel approach involving kinetic resolution of racemic LY213829 has been previously reported.[1] This route provides material of moderate enantiomeric purity (90% ee) and requires a chromatographic purification of enantioenriched **1**. We now report the synthesis of each enantiomer of LY213829 utilizing 2-methylbenzylamine in formation of the 4-thiazolidinone ring. Chemoselective removal of the 2-methylbenzyl group affords enantioenriched LY213829.

The five-step synthesis of (-)-LY213829 is shown in the Scheme. Racemic rhodanine derivative **6** was prepared in two steps using a modification of the literature procedure.[1] Condensation of commercially available aldehyde **2** and rhodanine **3** provided the benzylidene rhodanine adduct **4** in high yield. Treatment of adduct **4** in toluene (0.6 M) at reflux with 1.2 equiv of dihydropyridine **5**[2] afforded rhodanine **6** without observable byproducts.[3] Ohno and coworkers have reported that silica gel catalyzes reductions using dihydropyridine **5**.[4] In our case, silica gel was not necessary on large scale as the rate acceleration for a concentrated reaction (0.6 M, 2 h with 0.5 mass equivalents of silica gel vs. 5.5 h without) was less than for a dilute reaction (0.07 M, 4 h with 0.5 mass equivalents of silica gel vs. >24 h without). A larger rate acceleration at lower concentrations is consistent with Ohno's original proposal that silica gel increases the "local concentration" of the reactants.[4a]

Rhodanine **6** was hydrolyzed to racemic thiol acid **7** using 2M NaOH at reflux. Attempted classical resolution of acid **7** via salt formation with chiral amines was unsuccessful. We then considered the possibility that a chiral amine could be incorporated into the 4-thiazolidinone ring and the resulting diastereomers might be separable. Success of this approach required a method to cleave the auxiliary C-N bond in the presence of a C-S bond α to an amide carbonyl. Despite our concern that 2-methylbenzylamine would provide an amide which would be difficult to hydrogenolyze,[5] the low price and wide availability of this amine in both enantiomeric forms warranted its evaluation. Using a modification of the literature procedures,[6] racemic thiol acid **7** was treated with paraformaldehyde and (*R*)-2-methylbenzylamine in toluene at reflux to afford a 1:1 mixture of diastereomeric (5*S*,3α*R*)-thiazolidinone **8a** and (5*R*,3α*R*)-thiazolidinone **8b** in quantitative mass balance.

Scheme

8a (5*S*,3α*R*)
8b (5*R*,3α*R*) in filtrate
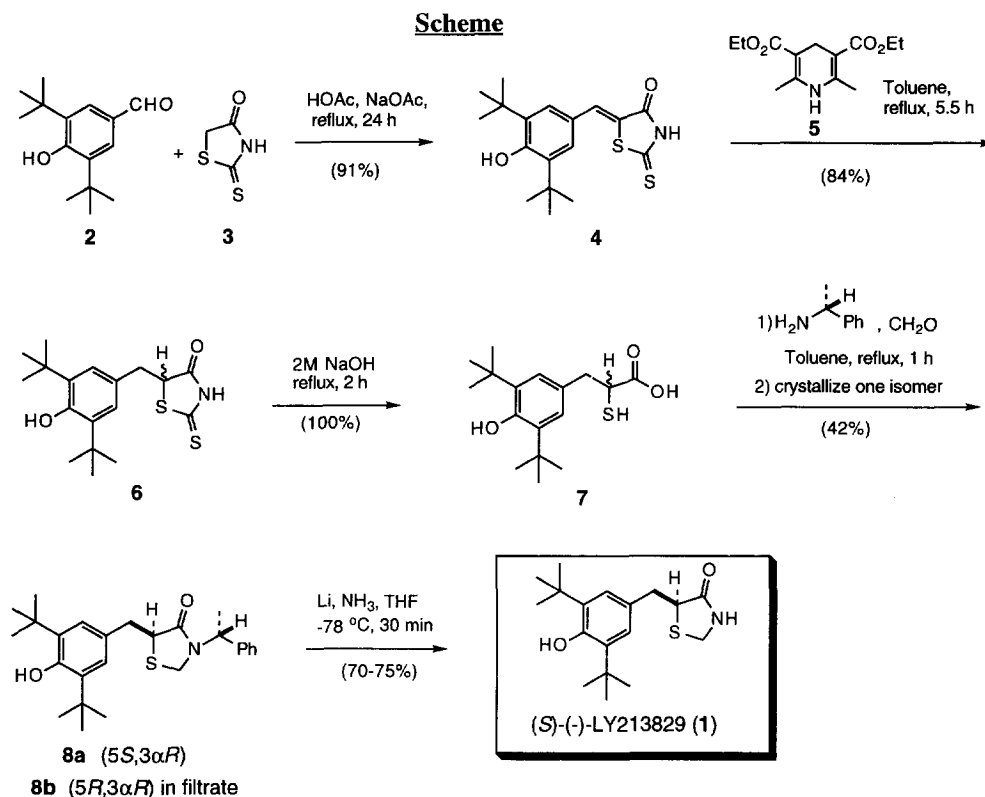
Filtration through silica gel to remove baseline material and recrystallization from hexanes afforded diastereomer **8a** in 42 % yield (**8a**:**8b** = 99 : 1 by HPLC). The relative and absolute stereochemistry of thiazolidinones **8a** and **8b** (and ultimately the absolute stereochemistry of the enantiomers of LY213829) was established by a single crystal x-ray structure determination of **8a**.[7] Quantities of diastereomer **8b** could be obtained from the above filtrate by crystallization. Alternatively, the filtrate could be treated with base under thermodynamic (NaOEt, EtOH) or kinetic (LDA, THF) conditions to afford a 1:1 mixture of **8a** and **8b** which upon crystallization afforded an additional 16% yield of **8a**. In addition to thiazolidinones **8a** and **8b**, the corresponding *p*-nitro analogs **9a** and **9b** were prepared using (*R*)-2-methyl-*p*-nitrobenzylamine. The *p*-nitro thiazolidinones **9** might be easier to cleave under hydrogenolytic conditions than thiazolidinones **8**. The reactivity of the mixture of **9a** and **9b** was compared with **8a** under the conditions described below.

9a,b
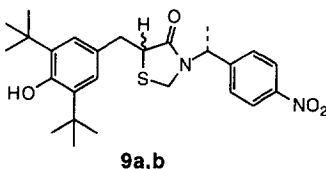
Use of (*R*)-2-methylbenzylamine in the cyclization reaction followed by crystallization provided an efficient method for "resolving" thiol acid **7** and assembling the 4-thiazolidinone ring in one operation.[8] We next

directed our attention toward the challenge of cleaving the C-N bond chemoselectively. Treatment of thiazolidinone **8a** in acetic acid at 25 °C with 1 atm of H_2 and Pd/C resulted in no reaction.[5] Under more forcing hydrogenolytic conditions (acetic acid, HCl, 1 atm H_2, Pd/C, 100 °C) decomposition occurred. When *p*-nitro thiazolidinones **9a** and **9b** were subjected to similar conditions, reduction of the nitro group to the amino group was facile but C-N cleavage to afford compound **1** was not observed. When thiazolidinone **8a** was treated under acidic conditions (formic acid, 95 °C or trifluoroacetic acid, 65 °C),[9] removal of a *t*-butyl group from the phenol ring was observed without removal of the 2-methylbenzyl group.

Successful cleavage of benzylamides by dissolving metal reduction has been reported by a number of groups;[10] however, chemoselective C-N cleavage without cleavage of a C-S bond α to the amide carbonyl group has not been investigated. We were gratified to find treatment of thiazolidinone **8a** in 2:1 THF/NH$_3$ at -78 °C with 2 moles of lithium wire afforded crude (-)-**1** and about 5-10% of thiol **10**.[11] The unoptimized ratio of (-)-**1** to thiol **10** was somewhat variable over the course of several experiments. Purification of the crude reduction product by chromatography on silica gel afforded (-)-**1** in 70-75% yield and >98% ee. Treatment of *p*-nitro thiazolidinones **9a** and **9b** with a large excess of lithium in THF/NH$_3$ did not afford any LY213829. Presumably initial reduction of the nitro group inhibits cleavage of the C-N bond.
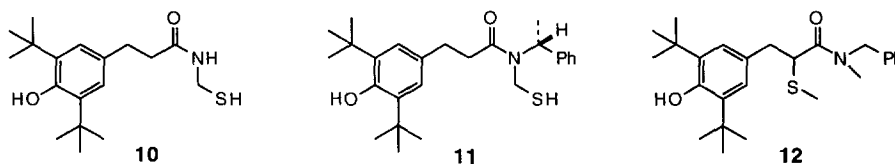
In addition to thiol **10**, crude (-)-**1** contained minor amounts of starting material and thiol **11**[12] where C-S bond cleavage has preceded C-N bond cleavage. Detection of thiol **11** suggests that the major byproduct **10** can arise from further reduction of product (-)-**1** or intermediate **11**. When 4.5 equiv of lithium is used in the reduction, conversion of initially formed (-)-**1** to **10** is quite slow indicating that the preferred route to thiol **10** may be via intermediate **11**. Other metals were surveyed to determine whether production of thiol **10** could minimized. Use of sodium in ammonia gave a better selectivity early in the reaction; however, if sodium was added until 5% starting **8a** remained, the ratio of **1** to thiol **10** was similar to that obtained with lithium. Use of calcium in ammonia gave higher levels of thiol **10** than sodium or lithium despite the fact that calcium has been recommended as a more selective reducing agent due its lower reduction potential.[13] Perhaps as suggested by Doumaux,[13c] the product selectivity is more related to interaction of the reaction intermediates with the metal cation than to the reduction potential of the metals themselves.

The mechanism of benzylamide cleavage presumably entails addition of one electron to the phenyl moiety followed by scission of the C-N bond to afford an amide anion and a benzylic radical. Addition of a second electron affords a benzylic anion which is protonated by the phenolic proton to afford ethylbenzene. Cleavage of the C-S bond could be realized by addition of an electron to the amide carbonyl followed by bond rupture and addition of a second electron. We expected that addition of electrons to the phenyl ring would occur more readily than addition to the amide carbonyl. Our results with cyclic thiazolidinone **8a** are consistent with this hypothesis, although C-S bond cleavage is a significant side reaction. Lithium and ammonia reduction of the acyclic analog **12** showed a preference for C-S over C-N cleavage. This indicates that addition of electrons to amide carbonyl groups may be facile. Perhaps in cyclic substrate **8a**, poor overlap between the C-S σ-bond and the π-system of the intermediate radical anion makes C-S bond cleavage less favorable. Further studies using benzylic amide analogs of cyclic 4-thiazolidinone **8a** are in progress.

In summary, (*R*)-2-methylbenzylamine has been used to "resolve" thiol acid **7** and assemble the 4-thiazolidinone ring in one step. Reductive removal of the 2-methylbenzyl group has been achieved in the presence of a readily hydrogenolyzed C-S bond. The overall yield of (-)-LY213829 (**1**) prepared by this five-step route is 25% from aldehyde **2**. By substituting (*S*)-2-methylbenzylamine in this process, (+)-LY213829 has been prepared in an analogous fashion.

ACKNOWLEDGEMENT

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2. Prepared by literature procedure: Singer, A.; McElvain, S. M. *Organic Syntheses*, Coll. Vol. 2, **1943**, 214.

3. Treatment of **4** with hydride reagents or under catalytic hydrogenation conditions did not provide **6** cleanly.

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7. Compound **8a** crystallized from ethyl acetate/hexanes in the orthorhombic space group $P2_12_12_1$ with a unit cell having the dimensions a = 10.195(7) Å, b = 14.603(3) Å, c = 16.336(4) Å and a calculated density of 1.162 g / cm^{-3}. The data was collected on an automated four-circle diffractometer using monochromatic copper radiation. A total of 1922 reflections with 2Ø less than 116.0° were measured. The structure was solved using direct methods and was refined by least-squares with anisotropic temperature factors for all atoms except hydrogen. All hydrogen atoms were included at calculated positions. A final R index of 0.042 was obtained for 1771 observed reflections.

8. Primary amines (anhydrous or aqueous solutions) afforded high yields of 4-thiazolidinone products. For comparison, treatment of **7** with paraformaldehyde and ammonium hydroxide afforded LY213829 in <5% yield.

9. Cleavage of a 2-methylbenzylamide at 60 °C in formic acid has been reported, see: Chen, S. Y.; Joullie, M. M. *J. Org. Chem.* **1984**, *49*, 1769-1772.

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11. Thiol **10** was isolated by silica gel chromatography followed by crystallization and was characterized by IR, ^{1}H and ^{13}C NMR, MS and elemental analysis. The solid thus obtained was stable toward air oxidation or loss of thioformaldehyde at room temperature.

12. Thiol **11** could be observed by HPLC and by ^{1}H NMR spectroscopy in the crude reaction mixture. However, chromatography followed by crystallization afforded the corresponding disulfide which was characterized by IR, ^{1}H and ^{13}C NMR, FAB MS and elemental analysis.

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