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Catalytic dissymmetrization of *meso*-2-imidazolidinones: alternative route to chiral synthons for 1,2-diamines

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Abstract—The chiral functionalization of a simple heterocycle, 1,3-dihydro-2-imidazolone, was achieved by the highly enantioselective monodeacylation of *meso*-1,3-diacetyl-2-imidazolidinones via an oxazaborolidine-catalyzed borane reduction. This kinetically controlled dissymmetrization is sufficiently effective to provide a synthetic route to either enantiomer of (4*S*, 5*S*)- or (4*R*, 5*R*)-4,5-dimethoxy-2-imidazolidinone derivatives, which serve as chiral synthons for *threo*-1,2-diamines.

The simple heterocycle, 1,3-dihydro-2-imidazolone,[1] has proven to be a promising building block for 1,2-diamine skeletons, which are found as structural units in bioactive compounds of medicinal interest[2] and chelating ligands for metal catalysts.[3] We recently reported on the preparation of versatile chiral synthons for the 1,2-diamines, (4*S*,5*S*)- and (4*R*,5*R*)-4,5-dimethoxy-2-imidalidinone (DMIm) derivatives, using 1,3-dihydro-2-imidazolone as the starting material.[4] Both methoxy groups of the DMIm synthons can readily be replaced with primary to tertiary alkyl groups and aryls with full retention of configuration in a stepwise manner. Subsequent ring-opening provides a versatile route to optically active *threo*-1,2-diamines. The reported synthesis of the chiral DMIm synthons involves an efficient, but rather tedious step for optical resolution, in which stoichiometric amounts of (1*S*,2*R*)-2-methoxy-1-apocamphanecarboxylic acid (MAC-acid) are used.[5]

In this paper, we describe a catalytic dissymmetrization approach to the preparation of DMIm synthons, in which the enantioselective *N*-monodeacetylation[6] of *meso*-1,3-diacetyl-2-imidazolidinones (**3**) by an oxazaborolidine-catalyzed borane reduction is a key step.

A series of *meso*-4,5-dialkoxy-2-imidazolidinones (**2a**–**e**) were conveniently prepared by treatment of (DL)-*trans*-4,5-dimethoxy-2-imidazolidinone (**1**), which is easily produced by the 4,5-dibromination of 1,3-diacetyl-2-imidazolone with bromine followed by methanolysis, with the *meso*-1,2-diols in the presence of $BF_3{\cdot}OEt_2$ at 0 °C to room temperature (Table 1). The *cis*–'*anti*'–*cis* structures for the cyclized *meso*-products **2** shown here are based on the X-ray crystal analysis of compound **6**.[7] This BF_3-catalyzed procedure was equally applicable to condensation reactions with *meso*-hydrobenzoin and catechol, while ethylene glycol failed to give the cyclized *meso*-products (**2f**), resulting in the formation of substantial amounts of polymeric adducts. *meso*-4,5-Ethylenedioxy-2-imidazolidinone (**2f**) was synthesized by alternate route involving treatment of 1,3-diacetyl-2-imidazolone with NBS in 2-*tert*-butoxyethanol, followed by cyclization in the presence of $BF_3{\cdot}OEt_2$.[8] The subsequent acetylation of compounds **2a**–**f** thus obtained gave *meso*-1,3-diacetyl-2-imidazolidinones (**3a**–**f**), which were used in the kinetically controlled dissymmetrization reactions.

The reaction conditions for the deacetylation of *meso*-1,3-diacetyl-2-imidazolidinone (**3b**) were examined, in an attempt to optimize the oxazaborolidine-catalyzed dissymmetrization (Table 2). The BH_3–SMe_2 complex was the borane reagent of choice. Thus, the use of the BH_3–SMe_2 complex (0.7 equiv) in the presence of the aminoalcohol **4** (0.2 equiv) at 20 °C gave promising results, while the THF complex resulted in a lower yield

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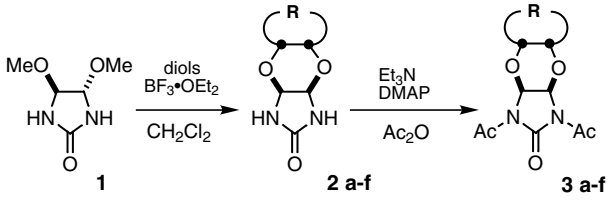
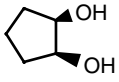
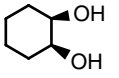
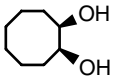
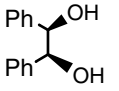
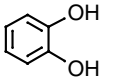
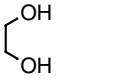
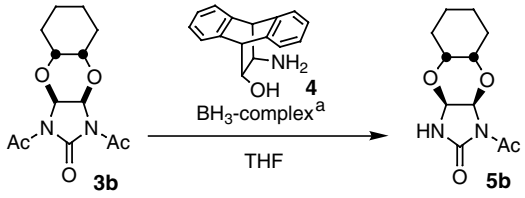
Table 1. Preparation of *meso*-1,3-diacetyl-4,5-dialkoxy-2-imidazolidin



Entry	Diols	R		2[a] (%)	3 (%)
1		–$(CH_2)_3$–	(**a**)	74 (14)	85
2		–$(CH_2)_4$–	(**b**)	75 (8)	88
3		–$(CH_2)_6$–	(**c**)	91	61
4		**Ph**, **Ph**	(**d**)	60 (15)	70
5		***o*-Phenylene**	(**e**)	22 (58)	80
6		**H**, **H**	(**f**)	0 (88)[b]	

[a] The reaction was performed by the dropwise addition of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 into a stirred equimolecular mixture of 2-imidazolidinone (**1**) and *meso*-diol in CH_2Cl_2 at room temperature. Recovery yields were in parentheses.
[b] See Ref. 8.

Table 2. Enantioselective monodeacetylation by aminoalcohol-catalyzed borane reduction



Entry	BH_3-complex (equiv)	Temp (°C)	Time (h)	Yield[b] (%)	Ee[c] (%)
1	–THF (0.7)	20	2	34	94
2	–SMe_2 (0.5)	20	1	47 (6)	93
3	–SMe_2 (0.7)	20	1	60 (9)	93
4	–SMe_2 (1.2)	20	1	60 (6)	93
5	–SMe_2 (1.7)	0	0.5	55	98
6	–SMe_2 (0.7)[d]	20	5	68 (11)	93
7	–Et_3N (0.7)	20–40	3	0 (100)	—
8	Thexylborane (0.7)	20	1	47 (22)	70
9[e]	–SMe_2 (0.7)	20	5	39 (15)	72

[a] To a stirred solution of **4** (0.2 equiv) and BH_3-complex (0.2 equiv) in THF was added a mixture of **3b** and another portion of BH_3-complex.
[b] Recovery yield in parentheses.
[c] Determined by HPLC as the *N*-Cbz derivatives.
[d] Borane-complex was added portionwise.
[e] (1*S*,2*R*)-1-Amino-2-indanol was employed instead of **4**.

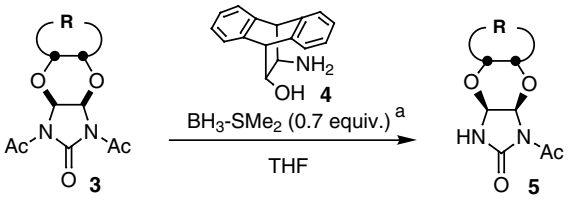
and the Et_3N complex was completely unreactive (entries 1 and 7). Lower amount (0.1 equiv) of aminoalcohol **4** gave slightly low yield (51%) and selectivity (89% ee). A reaction with BH_3–SMe_2 complex (1.7 equiv) at

0 °C gave the highest enantioselectivity of 98% ee (entry 5) but lower yield. The portionwise addition of the borane reagent at 30–60 min intervals further improved the efficiency of the reaction (entry 6). A conventional aminoalcohol, such as (1*S*,2*R*)-1-amino-2-indanol, was not as effective as a catalyst resulting in an enantioselectivity as low as 72% ee (entry 9). As summarized in Table 3, when *meso*-1,3-diacetyl-2-imidazolidinone derivatives **3a**–**f** were treated with BH_3–SMe_2 complexes (0.7 equiv) in the presence of (−)-aminoalcohol **4** (0.2 equiv), the enantioselective monodeacetylation proceeded smoothly at 20 °C to give monoacetyl derivatives in excellent enantioselectivity, except for compound **3f** which resulted in a much poorer enantioselectivity and yield. Compound **3e**, produced using catechol in place of the *meso*-diols served equally well, providing a selectivity in excess of 90% ee. The absolute configurations of the products were determined on the basis of X-ray crystal analyses of the *N*-(1*S*,2*R*)-MAC derivatives **6**. From the yield and selectivity, we accepted **3b** as the *meso*-2-imidazolidinone of choice and examined further conversions.

Unfortunately, **5b** failed to react with organocuprate as we had reported for 4,5-dimethoxy-2-imidazolidinones,[4] we tried to convert the acetal moiety of **5b** to *O*-methyl acetals. Both enantiomers of the 4,5-dimethoxy-2-imidazolidinone derivatives (**9** and ***ent*-9**) were synthesized by the straightforward manipulation of the kinetically discriminated product **5b**, including stepwise methanolysis of acetal moieties catalyzed by cationic ion-exchange resin, Amberlyst® 15.

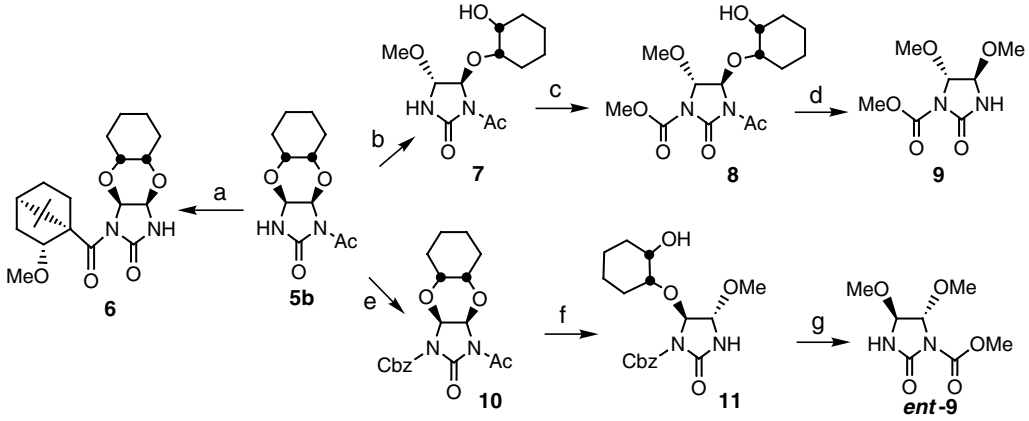
Thus, the Amberlyst®-catalyzed methanolysis of **5b**, which were readily obtained in an optical pure form by single recrystallization, proceeded smoothly only in part to give an equilibrium mixture of compounds **5b** (41%) and **7** (46%). This is also the case for deacetylated compound of **10** (45%) and compound **11** (37%).

Table 3. Enantioselective monodeacetylation of *meso*-1,3-diacetyl-2-imidazolidinones



Entry	Compound	Time (h)	Product	Yield[b] (%)	Ee[c] (%)
1	**3a**	2	**5a**	50 (14)	93
2	**3b**	5	**5b**	60 (9)	93
3	**3c**	5	**5c**	60 (5)	92
4	**3d**	5	**5d**	53 (18)	89
5	**3d**	5	**5e**	63 (8)	90
6	**3f**	5	**5f**	42 (32)	34

[a] To a stirred solution of **4** (0.2 equiv) and BH_3–SMe_2 (0.2 equiv) in THF was added a mixture of **3** and another portion of BH_3–SMe_2 at 20 °C.
[b] Recovery yield in parentheses.
[c] Determined by HPLC as the *N*-Cbz derivatives except for **5d** and **5e**, which were directly determined.



Scheme 1. Reagents and conditions: (a) (i) MAC-Cl, Et_3N, CH_2Cl_2, 80%, (ii) Cs_2CO_3, MeOH, 91%; (b) Amberlyst 15, MeOH,50 °C, 41%; (c) $ClCO_2Me$, Et_3N, CH_2Cl_2, 98%; (d) Amberlyst 15, MeOH, reflux, 72%; (e) Cbz-Cl, Et_3N, CH_2Cl_2, 96%; (f) Amberlyst 15, MeOH, reflux, 45%; (g) (i) $ClCO_2Me$, Et_3N, CH_2Cl_2, 97%, (ii) Pd–C, Amberlyst 15 MeOH, H_2, rt.

Methanolysis occurred exclusively at 4-position, the unprotected NH-side of 2-imidazolidinone heterocycles, in perfect *regio* and *trans* selectivity.

Methoxycarbonylated compound **8** underwent deacetylation and methanolysis to give (4*R*,5*R*)-*N*-methoxycarbonyl-4,5-dimethoxy-2-imidazolidinone **9** under reflux condition with Amberlyst® 15.

On the other hand, *N*-Cbz derivative **10** underwent deacetylation and methanolysis to give the equilibrium mixture of deacetylated compound of **10** and compound **11**. After protection of the NH moiety by methoxycarbonylation, hydrogenolysis on Pd–C in the presence of Amberlyst® 15 yielded the (4*S*,5*S*)-dimethoxy compound ***ent*-9**.

These mono-protected dimethoxy-2-imidazolidinones **9** and ***ent*-9** can be used as chiral synthons for 1,2-diamines similar to the *N*-methoxyapocamphancarbonyl-4,5-demethoxy derivatives (MAC-derivatives).[4]

In summary, we reported on the development of a catalytic process for the efficient discrimination between two enantiotropic acyl groups of *meso*-1,3-diacetyl-2-imidazolidinones, thus providing a facile synthetic route to chiral synthons for *threo*-1,2-diamines (Scheme 1).

References and notes

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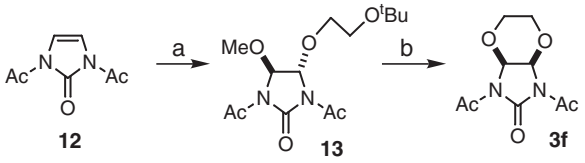
6. (a) Hashimoto, N.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1998**, *39*, 6317–6319; (b) Yokoyama, K.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1999**, *40*, 6285–6288(c) *N*-Monodeacetylation of 1,3-diacetyl-4,5-dimethoxy-2-imidazolidinone showed poor results.
7. Crystal data for **6** (mp 227 °C): monoclinic, $P2_1$, a = 14.028(1) Å, b = 13.029(1) Å, c = 10.012(2) Å, V = 1966.1(4) Å^3, Z = 2. The structure was refined to the R value of 0.037. We are much indebted to the Yoshitomi Research Laboratories, Yoshitomi Pharmaceutical Ind. Ltd (Fukuoka, Japan) for this X-ray crystallographic analysis.
8. Compound **3f** was readily synthesized via 4,5-dialkoxy-2-imidazolidinone **13** derived from 1,3-diacetyl-2-imidazolone (**12**) and NBS in the presence of ethylene glycol mono *tert*-butyl ether.



a: (i) $HOCH_2CH_2O^tBu$, NBS, dioxane, 77%, (ii) Et_3N, Cs_2CO_3, MeOH, 81%
b: (i) $BF_3{\bullet}OEt_2$, CH_2Cl_2, 65%, (ii) Et_3N, DMAP, Ac_2O, 88%