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Rigid Aminoalcohol Backbone as a Highly Defined Chiral Template for the Preparation of Optically Active Tertiary α-Hydroxyl Acids

Chris H. Senanayake,* Kevin Fang*, Paul Grover, Roger P. Bakale, Charles P. Vandenbossche and Stephen A. Wald
Chemical Research and Development, Sepracor Inc., 111 Locke Drive, Marlborough, MA 01752, USA

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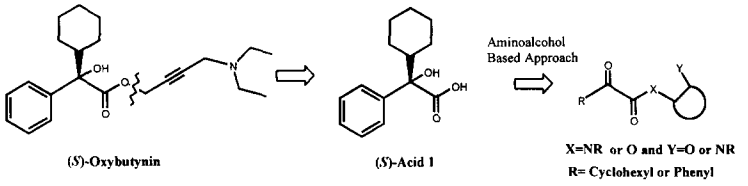
Abstract: *Constrained aminoalcohol derived-ketoester or amides have provided a new entry for the production of enantiopure acid 1 for (S)-oxybutynin.*

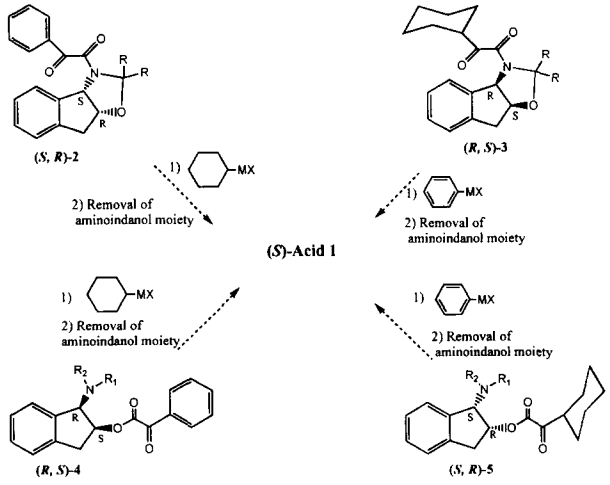
Tertiary hydroxy esters are highly important intermediates in the asymmetric synthesis of a variety of medicinal agents[1] and natural products.[2] For example, racemic oxybutynin (ditropan) a widely prescribed muscaronic receptor antagonist for the treatment of urinary incontinence contains a tertiary hydroxyl moiety. It has been documented that it exhibits classical antimuscarinic side effects such as dry mouth.[3] However, preliminary biological results suggest that (*S*)-oxybutynin displays an improved therapeutic profile compared to its racemic counterpart, and is currently in clinial trials. Interestingly, most of the muscarinic receptor antagonists comprise of tertiary α-hydroxy acid as a key component.[1,4] It has been revealed in the literature that the organometallic addition to cyclohexane based auxiliaries of ketoesters serve as the method of choice for the preparation of such optically enriched tertiary α-hydroxy acids.[5] An enormous number of alcohol based auxiliaries have been examined in this context; however, most of the auxiliaries are not general, not readily accessible and are often inefficient or lack diastereo-control.[6] Therefore, creating a tertiary alcohol center in which the absolute stereochemistry can be controlled by a defined chiral environment in the addition of organometallic reagents to ketones still represents a significant challenge.[7] We envisage that optically pure α-tertiary alcohol acids could be obtained from either ketoamide or ketoester-derived readily available constrained chiral aminoalcohols because they can serve as a highly organized chiral environment with certain organometallic reagents in the transition state for the alkyl- or aryl-addition process. Herein, we report on the C-1 amine or C-2 hydroxyl moiety of constrained *cis*-aminoalcohols as a highly defined chiral handle for the production of optically pure tertiary α-hydroxy acid **1**.



(*S*)-Oxybutynin (*S*)-Acid 1

Recent reports indicate that the rigid benzocycloalk-1-ene-derived vicinal *cis*-aminoalcohol platform plays a crucial role in asymmetric synthesis.[8] Interestingly, the generation of optically pure tertiary α-hydroxy acids have never utilized these inexpensive and valuable *cis*-aminoalcohols. As outlined in **Figure 1**, our plan was to take advantage of the C-1 amine or C-2 alcohol of *cis*-aminoindanol as a chiral handle and examine the diastereoselective cyclohexyl or phenyl Grignard addition process to the appropriate keto-moiety for generation of (*S*)-acid **1**.

Figure 1: Synthetic plan for the generation of enantiopure α-tertiary alcohol acid 1



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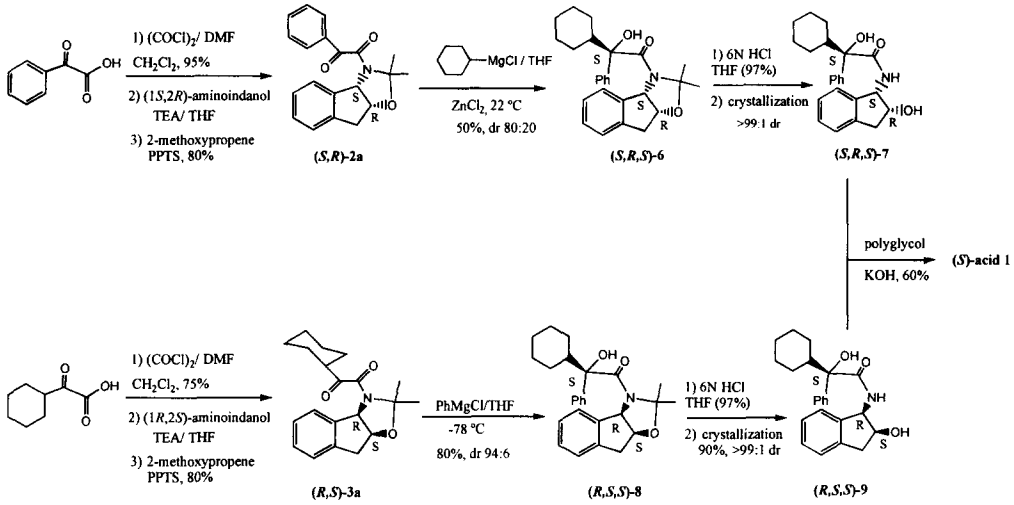
When the C-1 amine is utilized as a chiral handle, rigid tricyclic aminoindanol acetonide ketoamide (*S, R*)-**2a** and (*R,S*)-**3a** (where R= Me) were selected for the examination of diastereofacial Grignard addition process.[9] Substrates (*S, R*)-**2a** and (*R,S*)-**3a** were prepared as depicted in Scheme 2 in high overall yields.[10] First phenyl ketoamide (*S, R*)-**2a** was investigated in the presence of a variety of conditions with or without additives such as Zn^{2+}, Ti^{4+}, Mg^{2+}, $CuBr.Me_2S$ and $CeCl_3$. It is interesting to note that the addition of cyclohexyl Grignard with $ZnCl_2$ at room temperature provides the highest selectivity as 80:20 with a moderate yield (50%).[11] Without $ZnCl_2$, a complex mixture of products was observed. At low temperatures with or without $ZnCl_2$, the reactions proceeded extremely slowly. After mild acidic hydrolysis of the crude acetonide (*S,R,S*)-**6** to the corresponding diastereomeric amidoalcohols followed by crystallization provided >99:1, dr of the desired diastereomer as (*S,R,S*)-**7** (Scheme 2). On the other hand, we are gratified to disclose that when the cyclohexyl ketoamide (*R,S*)-**3a** was subjected to phenylmagnesium chloride in THF at -78 °C, high diasteroselectivity (>94:6, dr) with high yields resulted. The most favorable diasteroselective/temperature profile was found to be at -78 °C (-50 °C, 90:10, dr; 0 °C, 85:15, dr). Simple acidic hydrolysis followed by crystallization from EtOAc/ hexanes provided diastereomerically pure amidoalcohol (*R,S,S*)-**9** in >85% yield. (**Scheme 2**). However, attempts to hydrolyze the sensitive and hindered **6**, **7**, **8** or **9** with known conditions resulted in either decomposition or very low yield.[12] Fortunately, exposure of sterically congested compound (*R,S,S*)-**9** to polyglyclycol (ethylene glycol, diglyme or triglyme etc.) in the presence of KOH or NaOH at 130-140 °C provided ~60% yield with > 99% ee of (*S*)-acid **1**.[13] The recovery of *cis*-aminoindanol was >85% by assay.

Scheme 2:



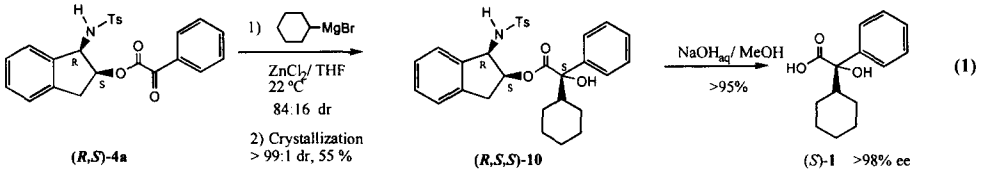
Since the hydrolysis of sterically congested compound (*S,R,S*)-**7** or (*R,S,S*)-**9** provided moderate yields of (*S*)-acid **1**, our attention was then focused on easily hydrolizable C-2 hydroxyl derived esters. It was anticipated that the Grignard addition process might give high selectivities, because the rigid aminoindanol backbone has a highly defined chiral environment. Recently, Ghosh and co-workers have exemplified this phenomena by demonstrating that N-tosylate derived aminoindanol esters undergo several excellent diastereoselective processes[8] for example, *syn* and *anti*-aldol,[14a] and reduction of ketoesters.[14b] As noted in **Table 1**, our focus was aimed at studying the role of C-1 amine ketoester derivatives (*R,S*)-**4** (**Figure 1**) in the Grignard addition process. When cyclohexyl Grignard addition to ketoester (*R,S*)-**4** was conducted without $ZnCl_2$ or $CeCl_3$ with ketoesters, diminished selectivities and yields were observed.

Table 1: Diasteroselective Cyclohexyl Grignard addition process with ketoester 4

Substrate	R_1	R_2	Cyclohexyl Grignard (Equiv).	Additives (Equiv.)	dr (^{1}H-NMR r	Yield (%)
4a	Ts	H	2.5	-------	67:33	65
4a	Ts	H	2.5	$ZnCl_2$ (0.3)	67:33	80
4a	Ts	H	2.5	$ZnCl_2$ (1.0)	68:32	75
4a	Ts	H	2.5	$ZnCl_2$ (2.5)	84:16	75
4a	Ts	H	2.5	$ZnCl_2$ (5)	84:16	85
4a	Ts	H	3.0	$CeCl_3$ (3)	80:20	70
4b	Ts	Me	1.5	$ZnCl_2$ (2.5)	83:17	80
4c	Me	Me	1.5	$ZnCl_2$ (2.5)	88:12	80

All reactions were conducted at 22 °C in THF.

Interestingly, in the presence of $ZnCl_2$ at ambient temperature, *N*-tosylate amino **4a**, N-methyl-N-tosylate amino **4b** or N,N-dimethylamino **4c** provided highly comparable asymmetric inductions with good yields. It is important to note that tosylate-derived ketoesters (*R,S*)-**4** are much more stable than the *N,N*-dimethyl counterpart. The ketoester (*R,S*)-**4b** with cyclohexyl Grignard addition provided crude addition products as an oily mixture and required further purification by chromatography. On the other hand, N-tosyl ketoester **4a** was crystalline, easy to prepare and the addition product was crystalline. Therefore, the (*R,S*)-**4a** was nominated as the ligand of choice for the optimization process in the preparation of (*S*)-acid **1**. Crude (*R,S,S*)-**10** from the reaction mixture can be crystallized with EtOAc/Hexane to provide >99% de with an overall yield of 55% from (*R,S*)-**4a** (equation **1**). The hydrolysis of diastereopure (*R,S,S*)-**10** with NaOH/ MeOH/ H_2O provided enantiopure acid (*S*)-**1** with a recovery of the auxiliary.



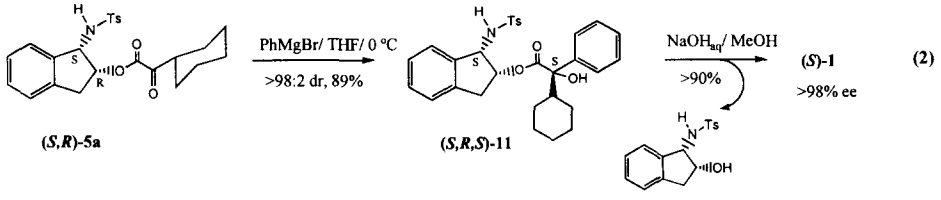
(1)

The salient feature of C-1 amine-derived ketoamide **2a** and **3a** with the Grignard addition process was that cylochexyl-derived ketoamide **2a** required magnesium coordination, and for phenyl derivative **3a**, a zinc coordinated transition state was essential in order to obtain maximum selectivities. Since tosylate derived C-2 phenyl ketoester **4a** behaves in a similar fashion to C-1 phenyl ketoamide **2a**, then verification of the similarities of Grignard addition process to C-1 and C-2 cyclohexyl derivatives required the preparation of cyclohexyl derived-ketoester (*S,R*)-**5a**. As depicted in **Table 2**, surprisingly comparable additive effects with phenyl Grignard addition for cyclohexyl C-1 amide and C-2 ketoesters were observed. Compound **5a** with phenyl magnesium bromide at 0 °C provided excellent diastereofacialselectivity (>98:2, dr) of (*S,R,S*)-**11** with an 89% yield. In the presence of $ZnCl_2$, either phenyl lithium or phenyl magnesium bromide gave an essentially non-diasterioselective process. Mild basic hydrolysis of crude (*S,R,S*)-**11** (>98:2, dr) provided >98% ee of (*S*)-acid **1** (equation **2**).

Table 2: Diasteroselective Cyclohexyl Grignard addition process with ketoester 5a

Phenyl M (Equiv.)	Additives (Equiv.)	dr (^{1}H-NMR ratios)	Yield %
MgBr (2.5)	$ZnCl_2$ (5)	52:48	85
MgBr (2.5)	$ZnCl_2$ (2.5)	50:50	85
MgBr (2.5)	---	>98:2	89
Li (2.5)	----	55:45	75
Li (2.5)	$ZnCl_2$ (5)	not determine	< 10

All reactions were conducted at 0 °C in THF.

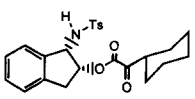


(2)

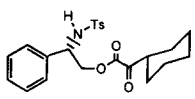
Encouraged by the outstanding stereocontrolled outcome of the indane-derived tosylate ketoester **5a**, the following conformationally related ketoesters **12** and **13** were prepared. Phenyl glycinol derivative **12** with PhMgBr/THF at 0 °C provided no-selectivity. On the other hand, homologous six-membered analogue **13** gave comparable results (99:1, dr) to the indane system. Surprisingly, substitution of N-tosyl group with N-BOC (**14**), or phthalimido moiety (**15**) provides essentially no-induction with PhMgBr in THF at 0 °C.

The viability of the high diastereoselective Grignard addition process was extended to other *N*-tosyl ketoesters and Grignards. When cyclopentyl ketoester **16** was exposed to PhMgBr/THF at 0 °C >98:2 diastereoselectivity of the corresponding tertiary hydroxyl ester (>85% yield) was obtained. Ketoester (*R,S*)-**4a** upon treatment with *p*-chlorophenyl magnesium bromide in the presence of $ZnCl_2$ at 22 °C provided excellent selectivity (>98:2 dr) of **17** in an 87% yield.

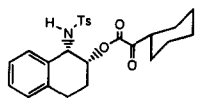
In conclusion, we have shown that either C-1 amine or C-2 alcohols of *cis*-aminoindanol or related constrained aminoalcohols can be utilized as a highly defined chiral handle for the preparation of enantiopure tertiary α-hydroxy acids *via* appropriate metal coordinated 1,1-dicarbonyl systems in the Grignard addition process. In our study, *N*-Tosyl-derived ketoesters provides the most expedient avenue to the preparation of optically pure (*S*)-acid **1.** The scope and limitations of generating tertiary alcohol centers of medicinally valuable targets with rigid aminoalcohol derivatives are being explored.



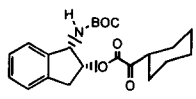
5a, >98:2 dr



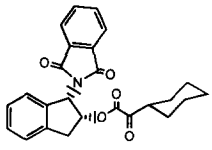
12, 50:50 dr



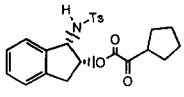
13, 99:1 dr



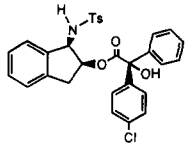
14, 55:45 dr



15, 57:43 dr



16, >98:2 dr



17, >98:2 dr

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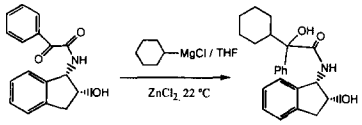
(9) (a) The addition of $C_6H_{11}MgBr$ with or without $ZnCl_2$ to amide (*S,R*)-**16** provided low de (<2%) of **6**. Therefore, conformationally locked acetonide ketoamide (*S,R*)-**2a** was considered (see reference 9b). (b) Askin, D.; Wallace, J. P.; Vacca, J. P.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771.



(*S,R*)-16 (*S,R,S/R*)-6

(10) Cyclohexyl keto acid was prepared by reacting cyclohexyl MgBr with diethyl oxalate to give 80-87% yield of ethyl cyclohexyl keto ester followed by basic hydrolysis. See reference: Weinstock, L. M.; Currie, R. B.; Lovell, A. V. *Syn. Comm.* **1981**, 943.

(11) (a) The major by-products were reduced forms of **2a**, and the structures were established by $NaBH_4$ reduction of (*S,R*)-**2a**. Recently Corey reported that isopropyl MgBr instead of addition to carbonyl group reduction was observed. See Corey, E. J.; Li, W.; Nagamitsu. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1677. (b) THF was the solvent of choice. For example, toluene and dioxane provided 60:40 dr and 80:20 dr respectively.

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