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Tetrahedron: *Asymmetry* 16 (2005) 1897–1900
Tetrahedron: *Asymmetry*

Asymmetric synthesis of α-methoxyarylacetic acid derivatives

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Received 26 March 2005; accepted 2 May 2005

Abstract—Stereoselective synthesis of a series of 2-aryl-2-methoxyethanols was achieved from inexpensive chiral pool tartaric acid employing a diastereoselective reduction of a symmetrical 1,4-diaryldiketone as the key step. 2-Aryl-2-methoxyethanols were enantioselectively prepared in 80–90% yield

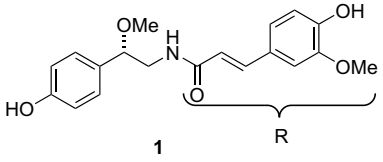
1. Introduction

The synthesis of chiral ligands, bio-active compounds and enantiomerically pure building blocks from inexpensive chiral sources is of significant importance because of the low cost and rich source of chirality associated with these chiral pool compounds.[1] With the advent of combinatorial and high-throughput techniques, there has been a growing interest in small molecules as therapeutic probes. Natural products such as **1** isolated from plant *Isodon excisus*, have been reported to display potent activity as apoptosis inhibitor.[2] Furthermore it has been demonstrated that **2** and **3**, identified from a screening of a combination of scaffolds based on core structure **1**, exhibited excellent selectivity in inducing apoptosis in cancerous white blood cells but is non-toxic towards non-cancerous white blood cells.[3,4] Coupled with their immense biological activity and potent pharmacological properties, demand for the rapid access to enantiomerically pure compounds of this type has increased. Herein, we report a general method for the synthesis of compounds based on α-arylmethoxy acid core from easily accessible chiral pool L-(+)-tartaric acid.

2. Results and discussion

A methodology for the synthesis of the title compounds is depicted in Scheme 1. We anticipated that the 1,2-diol unit of tartaric acid could be used as a masked aldehyde/acid synthon and as an appropriate chiral relay in modification of the existing carboxyl functionality. Thus, we identified the C_2-symmetric 1,4-diaryl-1,4-diols as the potential starting compounds. Protection of the 1,4-diol as its methyl ether followed by cleavage of the 2,3-diol unit should lead to α-methoxyarylacetaldehyde, which can either be oxidized or reduced to the acid or alcohol, respectively.

With this postulate, at the outset, we began the synthesis with bis-Weinreb amide **5**, prepared according to the literature procedure[5] from dimethyl-L-tartrate. The addition of aryl Grignard reagent to the bis-Weinreb amide **5** efficiently furnished the corresponding 1,4-diketones[6] **4a**–**d**. Diketones **4a**–**d** can also be obtained in moderate to good yields by the addition of a Grignard reagent to dimethylamide[7] **6**, which is readily accessible from tartaric acid on a large scale (Table 1).



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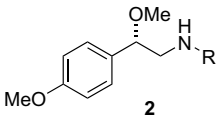

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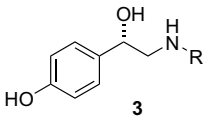

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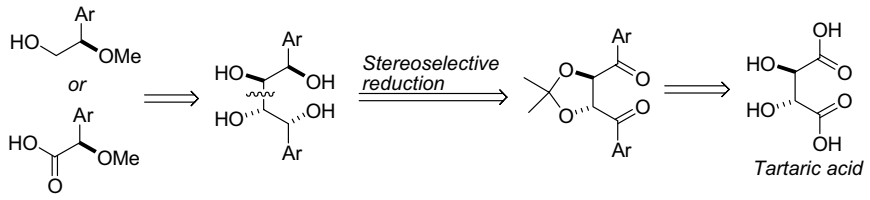
doi:10.1016/j.tetasy.2005.05.002



Scheme 1. Retrosynthesis for the preparation of α-methoxyarylacetic acid derivatives.

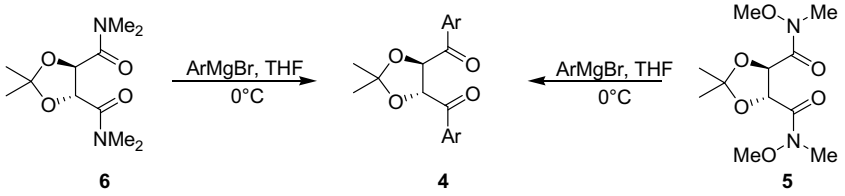


Table 1. Synthesis of 2,2-dimethyl-4,5-diaroyl-1,3-dioxalane **4** from **5** and **6**

Ar	Phenyl **4a**	4-Methoxyphenyl **4b**	4-Methylphenyl **4c**	3,4-Dimethylphenyl **4d**
Yield from **5**	86	83	89	85
Yield from **6**	77	69	53	50

We then studied the reduction of 1,4-dione **4a** as a model and examined the effect of various reducing agents on the formation of three possible diastereomeric diols (two C_2-symmetric **7a** and **8a** and one C_1-symmetric **9a**). The results are summarized in Table 2. Salient features of the reduction as a function of the reducing agent are as follows: (i) Use of $NaBH_4$ exhibited no preference in the formation of diastereomers, while use of a combination of $CeCl_3{\cdot}7H_2O$ and $NaBH_4$ produced a 2:1 mixture of **7a** and **8a**. (ii) $LiAlH_4$ produced the alcohols with only 10% de, while use of bulky reducing agents, such as $LiAl(O^tBu)_2H_2$ and $LiAl(O^tBu)_3H$, slightly improved the diastereomeric ratio. (iii) A moderate ratio (~4:1) was observed with K-Selectride as the reducing agent and **7a** as the major product, while a dramatic increment in the ratio 92:8 was observed using K-Selectride pre-complexed with 18-crown-6.

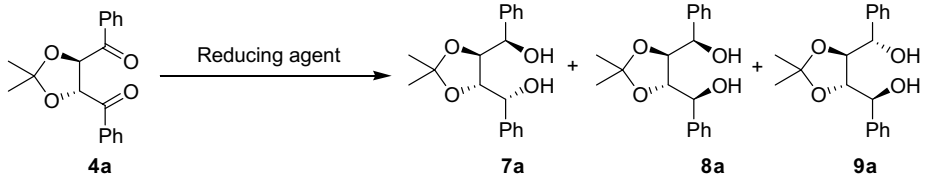


Table 2. Reduction of 2,2-dimethyl-4,5-dibenzoyl-1,3-dioxalane **4a**

S. no.	Reducing agent	Solvent	Temperature (°C)	Time (h)	Diastereomeric ratio[a]			Yield[b]
					7a	**8a**	**9a**	
1	$NaBH_4$	MeOH	−20	2	40[c]	47	13	94
2	$NaBH_4/CeCl_3{\cdot}7H_2O$	MeOH	−78	1	66	34	0	98
3	$LiAlH_4$	THF	0	1	55	45	0	95
4	$LiAlH_2(O\textit{t}\text{-Bu})_2$	THF	−78	1.5	68	27	5	96
5	$LiAlH(O\textit{t}\text{-Bu})_3$	THF	−20	1	63	32	5	90
6	L-Selectride	THF	−78	1.5	67	33	0	96
7	K-Selectride	THF	−78	0.5	71	29	0	96
8	**K-Selectride/18-C-6**	**THF**	**−78**	**4.5**	**92**[c]	**8**	**0**	**94**

[a] Determined by ^1H NMR.
[b] Refers to combined yield of all diastereomers after chromatography.
[c] Determined by HPLC.

After optimizing the conditions for reduction, we applied the protocol for the reduction of representative aryl substituted diketones **4b–d**. As indicated in Table 3, in all cases, 1,4-diols were obtained with good diastereomeric ratio. Major diastereomer **7** was separated by column chromatography from the minor isomer **8**. Minor isomer **8** was oxidized quantitatively to the corresponding starting dione **4** with IBX,[8] thus enabling the process almost 100% for the formation of the major diastereomer. However, for ease of purification and estimation of dr by ^{1}H NMR, crude reaction mixtures of the alcohols were transformed in to their corresponding methyl ethers **10a–d**.

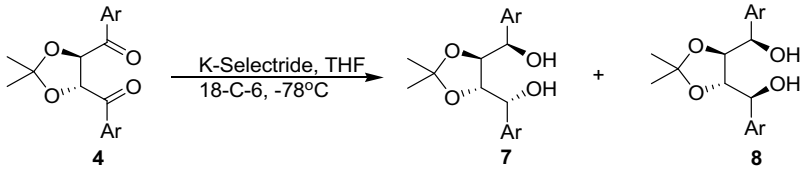


Table 3. Reduction of 2,2-dimethyl-4,5-diaroyl-1,3-dioxalane **4a–d** with K-Selectride

Ar	4a	4b	4c	4d
dr[a] **7**:**8**	91:9	86:14	89:11	91:9
Yield[b]	92	87	93	89

[a] Determined by ^{1}H NMR spectra of the crude reaction mixture of the diol or the corresponding dimethyl ether.
[b] Isolated yield of the mixture of diastereoisomers after chromatography as its methyl ether **10**.

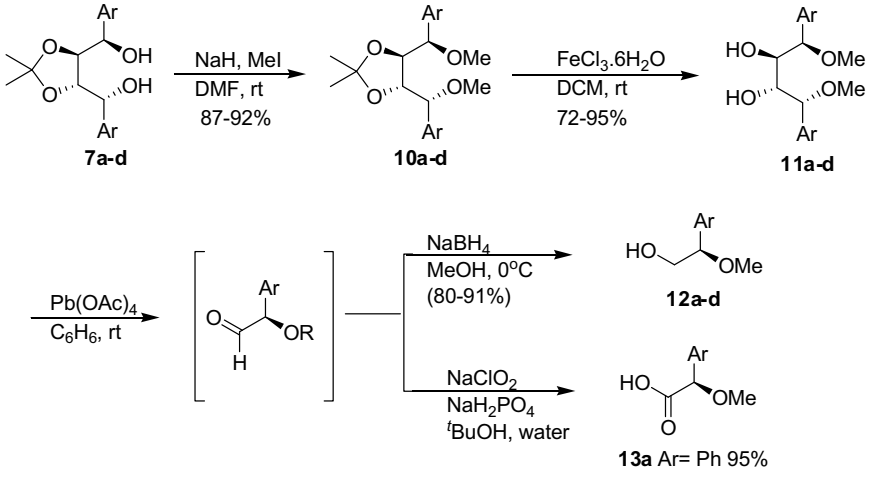
Facile deprotection of the acetonide of methyl ethers **10a–d** was effected with $FeCl_3$ in DCM[9] in 72–95% yield. Treatment of 1,4-dimethoxy-2,3-diols **11a–d** with $Pb(OAc)_4$ produced 2 mol of the corresponding aldehyde, which was either reduced with $NaBH_4$ to yield the alcohol or oxidized with $NaClO_2$ to furnish the corresponding acid. Stereochemical integrity was preserved in all these transformations and 2-aryl-2-methoxyethanols **12a–d** with a (1*R*)-configuration were produced with complete selectivity. The configuration at the newly formed stereogenic centre was further confirmed by comparing the specific rotation with the already known[10] methoxy alcohol **12a** and acid **13a**.[11]

3. Conclusion

In summary, a high yielding enantioselective approach to α-methoxyarylacetic acid derivatives was described from L-(+)-tartaric acid. Application of this strategy for the synthesis of other functionalized and non-functionalized hydroxy acids en route to a library of amino alcohols and diol moieties is underway. The evaluation of diols **10a–d**, which are analogues to TADDOL ligands[12] in asymmetric catalysis, is also under investigation.

Acknowledgements

We thank the Department of Science and Technology, New Delhi, for funding of this project. A.C. thanks CSIR, New Delhi, for a research fellowship.



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10. For **12a** $[\alpha]_D = -146$ (*c* 0.13, $CHCl_3$) for (*R*)-isomer. Lit.[11] $[\alpha]_D = -99.0$ (*c* 0.13, $CHCl_3$).
    For **13a** $[\alpha]_D = -141.8$ (*c* 0.13, $CHCl_3$) for (*R*)-isomer. Lit.[11] $[\alpha]_D = -144$ (*c* 1.03, $CHCl_3$).
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