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Selective addition of Grignard reagents to 2,3-*O*-isopropylidene bis-Weinreb tartaric acid amide

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Abstract—Controlled addition of Grignard reagents to tartaric acid derived bis-Weinreb amide **3** provides a facile, direct entry to desymmetrized 1,4-functionalized-*syn*-2,3-diol intermediates **4** and to C_2-symmetrical 1,4-diketones **5**. The synthetic versatility of this method is exemplified by short syntheses of the natural plant growth regulator **10** and the synthetically valuable cyclooctene derivative **13**.

The 1,2-diol subunit occurs in a large number of natural products of various classes including isoprenoids, alkaloids, polyketides and carbohydrate derivatives. Not surprisingly, methods for the asymmetric synthesis of both *syn*- and *anti*-1,2-diols have received much attention including catalytic asymmetric routes to *syn*-1,2-diols via Sharpless asymmetric dihydroxylation[1] and more recently *anti*-1,2-diols via the List proline catalyzed aldol reaction.[2] In order to prepare *syn*-1,2-diols through asymmetric dihydroxylation, one first has to assemble the requisite olefin of defined geometry as the substrate for the reaction. Tartaric acid **1** is a classic *chiral-pool* alternative for the rapid asymmetric synthesis of *syn*-1,2-diols. It is readily available in either enantiomeric form and possesses an innate *syn*-2,3-diol subunit. Tartaric acid is used extensively as a chiral precursor in the asymmetric synthesis of natural and non-natural products[3] as well as C_2-symmetrical molecules including chiral ligands.[4] Most literature methods for the differentiation of the 1,4-carboxylate residues on tartaric acid derivatives involve reaction on a 2,3-protected derivative (*O*-benzylidene or acetonide) via the intermediacy of a reduced 1,4-diol. Selective mono-protection[5] of one alcohol residue and re-oxidation of the remaining alcohol to the aldehyde allows for subsequent elaboration. The efficiency and versatility of the tartrate route would be greatly improved if controlled differentiation of the two carboxyl groups at C1 and C4 were possible directly at the oxidation level of the carboxylic acid leaving valuable functionality at both ends for subsequent manipulation.

The direct differentiation of the 1,4-carboxylate groups has been achieved via acylation (esterification, amination, etc.) of cyclic tartrate–anhydride derivatives.[6] Inherent limitations of this method are the necessity for chemoselective manipulations of the 1,4-carboxylate residues in the presence of two acetate esters, in addition to the impossibility of selective organometallic additions. The 2,3-*O*-isopropylidene-1,4-bis-Weinreb amide derivative of tartaric acid **3** has been reported and converted to C_2-symmetrical[7] 1,4-diketones using benzyl Grignard reagents as a route to HIV type-1 protease inhibitors. A recent report described one example of mono addition to this intermediate[8] with benzylmagnesium chloride allowing entry to a non-symmetrical 4-oxo-Weinreb intermediate, possessing differential functionality at the two carbonyl positions. We felt it worthwhile to investigate the generality of this procedure as a more direct asymmetric route to *syn*-2,3-diols retaining useful differentiable 1,4-functionality as well as C_2-symmetrical analogs. We now report that controlled organometallic addition to the bis-Weinreb amide **3** can provide good to excellent yields of differentiated non-symmetrical derivatives **4** as well as valuable C_2-symmetrical 1,4-diketone intermediates **5**.

L-Tartaric acid **1** is readily converted to dimethyl-2,3-*O*-isopropylidene tartrate diester **2** in one step on a 100 g scale.[9] Conversion of the diester to the bis-Weinreb amide **3** can be achieved using trimethylaluminum activation.[7] The bis-Weinreb derivative could also be prepared in similar yield directly from the diester using the method of Williams and co-workers.[10] The results of the addition reaction of various Grignard reagents to bis-Weinreb amide **3** are summarized in Table 1. For

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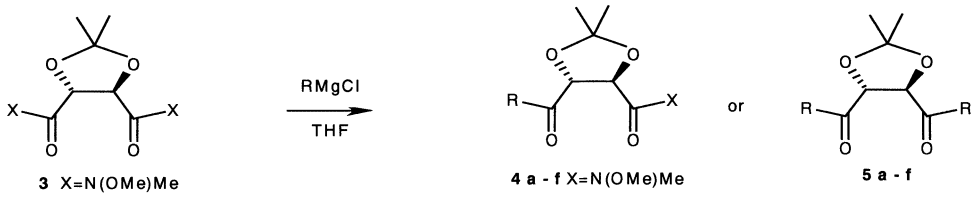
Table 1. Selective addition of Grignard reagents to bis-Weinreb amide **3**

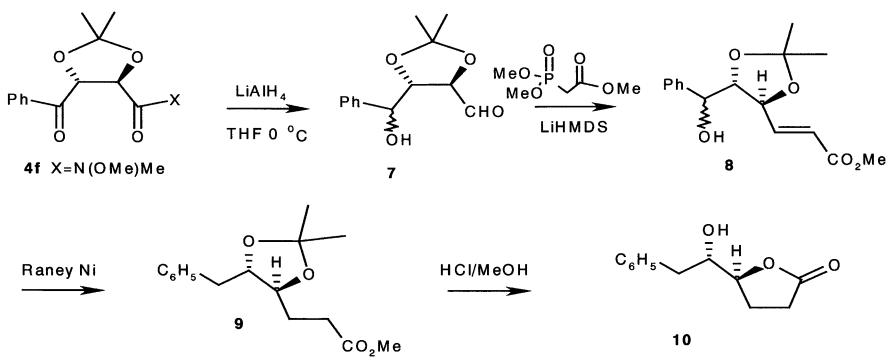


Entry	R-Mg-Cl (# equiv.)	Time (min)/Temp (°C)	Product	Yield (%)
1	Me (1.10)	30/0	**4a**	73
2	Me (2.20)	70/0	**5a**	92
3	Et (1.10)	15/0	**4b**	72
4	Et (2.20)	5/0	**5b**	98
5	^{i}Pr (4.00)	135/22	**4c**	77
6	^{i}Pr (4.00)	180/22[a]	**5c**	56
7	Allyl (1.50)	15/−78	**4d**	52
8	Allyl (3.00)	15/−78	**5d**	85
9	Bn (1.05)	45/−5	**4e**	62
10	Bn (3.00)	135/22	**5e**	73
11	Ph (1.05)	45/−5	**4f**	78
12	Ph (3.00)	135/22	**5f**	96

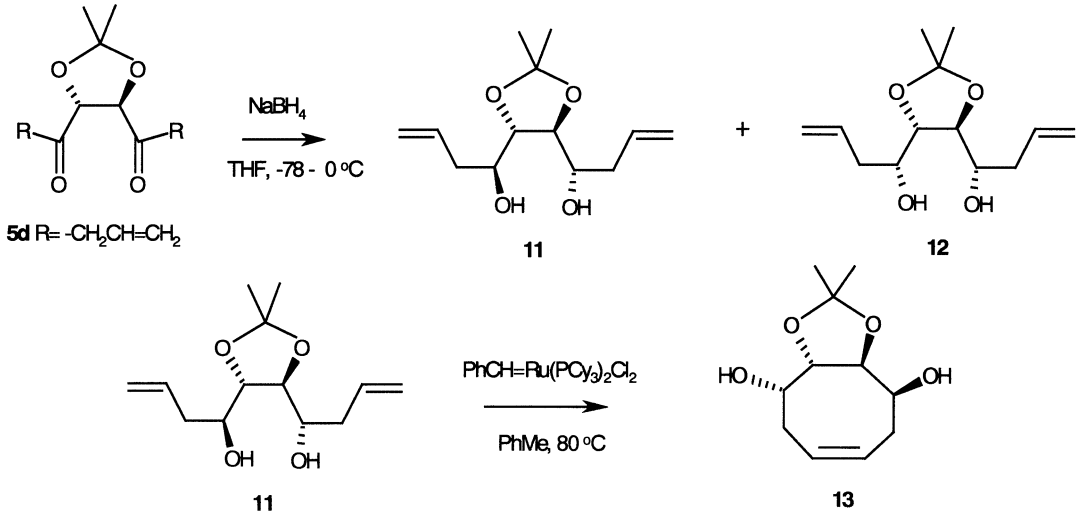
[a] Sonication was employed.

simple alkyl groups (entries 1 and 3) monoaddition occurs with good selectivity when one equivalent of Grignard is employed with only trace quantities of diketone detectable. Optimum yields of monoacyl derivatives were obtained employing 1.1 equivalent of the Grignard reagent. Monoaddition appears to be purely kinetically controlled as the reaction intermediates remain fully in solution. On the other hand, an excess of the alkyl Grignard (entries 2 and 4) is rapidly acylated leading to the diketone. Both mono and bis addition become sluggish as R increases from primary to secondary. Excess isopropylmagnesium chloride was slowly added giving **4c** (entry 5), while sonication was necessary to afford reasonable yields of the bis-isopropyl ketone **5c** (entry 6). In contrast to this, allylmagnesium chloride was acylated rapidly giving mixtures of **4d** and **5d** even when one equivalent of the Grignard reagent was employed. Lower temperatures and slightly more dilute conditions, however, afforded an acceptable yield of the mono allylketone (entry 7), while the symmetrical bis-allyl ketone could be obtained in high yield (entry 8). Both products **4d** and **5d** could be isolated using standard flash silica-gel chromatography, however extended contact with silica promoted the slow rearrangement to the thermodynamically more stable α,β-unsaturated mono- or bis-ketone derivatives. Selective mono- and bis-addition of benzyl and phenyl magnesium chloride to **3** (entries 9–12) could also be effected in good overall yields. No tertiary alcohols have been detected in any of the above reactions even when excess Grignard reagent is used.

The value of this direct de-symmetrization method is exemplified by a short asymmetric synthesis of the naturally occurring compound **10** containing a *syn*-diol sub-unit, Scheme 1. Compound **10** is the lactone form of a bacterial metabolite that has been shown to induce lateral root formation in various infected plant species.[11] The monophenyl ketone derivative **4f** was reduced with lithium aluminum hydride to give 4-hydroxyaldehyde **7** as a mixture of lactols, which was immediately reacted with the Horner–Emmons reagent to give the unsaturated ester **8** (3:1 mixture of benzylic alcohols). Reduction of the double bond occurred con-



Scheme 1. Synthesis of growth regulator **10**.



Scheme 2. Synthesis of cyclooctene **13**.

currently with hydrogenolysis of the benzylic secondary alcohol as expected to furnish the protected diol **9**. Hydrolysis of the *O*-isopropylidene acetonide under acidic conditions and concomitant transesterification provided the desired butyrolactone **10** directly (IR: C=O 1768 cm^{-1}). ^1H and ^{13}C NMR spectra as well as the optical rotation were in complete accord to those reported.[11] Of note here is the rapid assembly of the desymmetrized intermediate **9**[†] in three steps and 57% overall yield from **4f**.

In addition to the increasing recognition of cyclooctane derivatives as natural products, cyclooctene derivatives have proven to be synthetically valuable intermediates in their own right and are of considerable recent interest. Conversion of cyclooctenes to fused bicyclo [3.3.0]octanes may be carried out via an epoxidation–fragmentation strategy.[12] In addition, oxidation and amination protocols can provide stereochemically defined acyclic fragments as well as *O*- and *N*-heterocyclic derivatives.[13] It was therefore of interest to investigate the elaboration of tartaric acid into a chiral, C_2-symmetrical cyclooctene framework, as outlined in Scheme 2. Reduction of the bis-allyl ketone **5d** gave the C_2-symmetrical diol **11** as the major product along with a minor amount of the non-symmetrical diastereomer **12** (ratio **11**:**12** = 84:16). Ring-closing metathesis on **11** proceeded slowly in toluene at 80°C to give the synthetically valuable C_2-symmetrical cyclooctene derivative **13** in 59% yield.[‡] No protection of the hydroxyl groups[14] was necessary using the standard Grubbs catalyst under these conditions.[15]

In summary, we have shown that the tartaric acid derived bis-Weinreb amide **3** provides a general entry to useful desymmetrized keto-Weinreb intermediates **4** as well as C_2-symmetrical diketones **5** through the direct, selective functionalization of the carboxylate residues. The utility of this method in the synthesis *syn*-1,2-diols is exemplified by the synthesis of the natural butyrolactone **10** as well as a synthetically useful cyclooctene derivative **13**. Further application of this methodology towards the synthesis of natural products is currently in progress.

Acknowledgements

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[†] Compound **9**: ^1H NMR ($CDCl_3$): δ 7.2–7.3 (m, 5H), 3.91 (m, 1H), 3.74 (m, 1H), 3.67 (s, 3H), 2.97 (dd, J = 14.0, 6.6, 1H), 2.86 (dd, J = 14.0, 5.3, 1H), 2.3–2.5 (m, 2H), 1.6–1.8 (m, 2H), 1.38 (s, 3H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 174.1, 137.8, 129.8, 128.8, 126.9, 108.8, 81.3, 79.8, 77.6, 52.0, 39.5, 30.8, 28.2, 27.7.

[‡] Compound **13**: ^1H NMR ($CDCl_3$): δ 5.77 (t, J = 5.2, 2H), 4.26 (s, 2H), 4.18 (dd, J = 8.2, 4.2, 2H), 2.2–2.4 (m, 4H), 1.8 (br s, 2H), 1.45 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 128.1, 108.3, 76.7, 67.6, 29.1, 27.3.

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