An Enantioselective Decarboxylative Glycolate Aldol Reaction

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Glycolate aldol, decarboxylative, MAHT, syn diol, thioester

ABSTRACT: The development of catalytic enantioselective aldol reactions has been at the forefront of advancements in contemporary asymmetric methodology. Despite significant progress, the catalytic enantioselective synthesis of certain synthetically important motifs such as the ubiquitous aliphatic *syn*-diol remains a challenge. Herein, we report the application of a benzyloxy-functionalized malonic acid half thioester as an activated ester equivalent in a highly enantioselective glycolate aldol reaction. This robust method operates at ambient temperature, tolerates air and moisture, and generates CO_2 as the only by-product. The synthetic applicability of the method is demonstrated by the large-scale enantiodivergent synthesis of α-benzyloxy-β-hydroxybutyric acid thioester and its subsequent conversion to diverse polyoxygenated building blocks, deoxysugars, and the natural product (–)-angiopterlactone B.

Few asymmetric carbon–carbon bond forming reactions have reached the prominence of the aldol condensation in the synthesis of complex molecules. The asymmetric aldol reaction unites a carbonyl-derived enolate and an acceptor aldehyde to create a new carbon–carbon bond with the concomitant formation of two new stereogenic centers in a reliable and selective fashion. The glycolate aldol reaction, the condensation of an α-alkoxyacetate and an aldehyde, represents an important example of this transformation that allows for the stereocontrolled synthesis of enantiopure 1,2–diols. Vicinal *syn*-diols are a ubiquitous unit in carbohydrates and polyoxygenated natural products, in particular polyketides (Figure 1A).[1,2] While the stereoselective synthesis of *syn*-diols using a chiral auxiliary-based approach with preformed enolates is well established,[3] the catalytic enantioselective synthesis of these motifs remains challenging. Several catalytic enantioselective α-hydroxyacetyl aldol protocols have been reported using aromatic ketones,[4–6] or hydroxyacetone derivatives as the enolate partner.[7–9] However, these protocols have not found widespread application in synthesis due to the limited synthetic versatility of the products. Examples of the more synthetically useful catalytic, enantioselective glycolate aldol reactions with the carbonyl donor at the carboxylic acid oxidation state remain scarce.[10,11]

Mukaiyama-type glycolate aldol reactions that can deliver the 1,2–diol product in high selectivity have been reported by the Kobayashi and Denmark groups.[12–15] In the latter case, either *syn*- or *anti*-diol products could be attained by a chiral Lewis base-catalyzed addition of preformed glycolate-derived silyl ketene acetals to aldehydes (Figure 1B). The Trost group has pioneered the use of dinuclear zinc-ProPhenol catalysts for aldol-type transformations, including an aldol reaction using α-hydroxyketones as the carbonyl donor.[5] They subsequently reported a ProPhenol ((*S*,*S*)-**3**)-catalyzed *syn*-selective glycolate aldol reaction using *N*-acylpyrroles as activated ester equivalents (Figure 1C).[16] However, aliphatic aldehydes have proven to be troublesome substrates in these methods, delivering the corresponding *syn*–diol products (**2** & **4**) in moderate yield and stereoselectivity, thereby limiting the synthetic utility of these approaches. Therefore, the development of a new catalytic glycolate aldol reaction that provides efficient and selective access to synthetically important *syn*–diols is highly desirable.

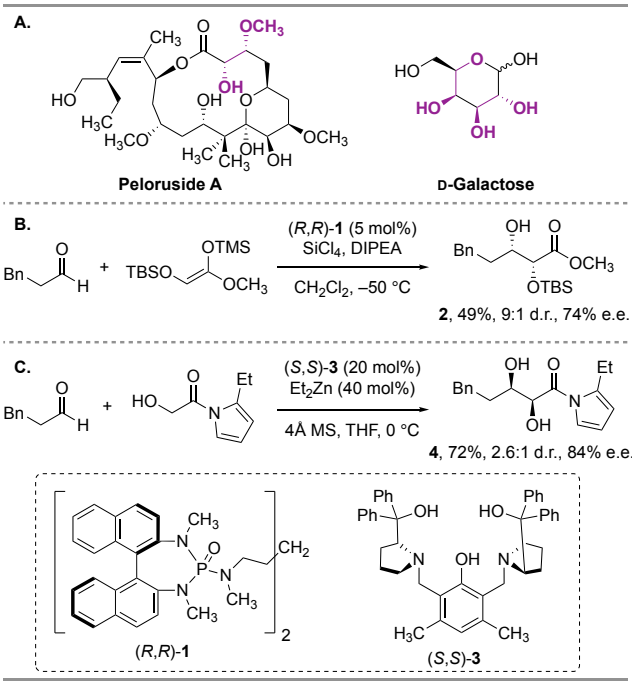


Figure 1. (**A**) Aliphatic *syn*-1,2-diols are a prevalent motif in natural products and carbohydrates. (**B**) Lewis base (*R*,*R*)-**1**-catalyzed Mukaiyama glycolate aldol (Denmark). (**C**) Zinc-ProPhenol (*S*,*S*)-**3**-catalyzed glycolate aldol (Trost).

Decarboxylative carbon–carbon bond forming reactions using malonic acid half thioesters (MAHTs) as ester enolate surrogates have become increasingly popular in asymmetric synthesis.[17] The presence of the additional carboxylic acid moiety on the MAHT overcomes common challenges associated with using thioesters as templates in asymmetric reactions. The 1,3-dicarbonyl unit can coordinate the catalyst to generate an activated, and more rigid thioester enolate nucleophile. Functionalized MAHTs have been successfully used as acetate,[18] propionate,[19,20] α-chloroacetate,[21] and α-fluoroacetate surrogates[22] in enantioselective aldol reactions. We previously reported a stereodivergent aldol reaction using alkyl-substituted MAHTs in the presence of a Ti(IV)-salen catalyst.[20] Decarboxylative addition of MAHT **6** to diverse aldehydes provided the corresponding aldol products in high yield and stereoselectivity (Figure 2A). Desirable features of the method include easy set-up, scalability, and high atom economy. Herein, we report that this mild method tolerates α-alkoxy-functionalized MAHTs, thereby enabling the challenging synthesis of *syn*-1,2-diols through a catalytic glycolate aldol.

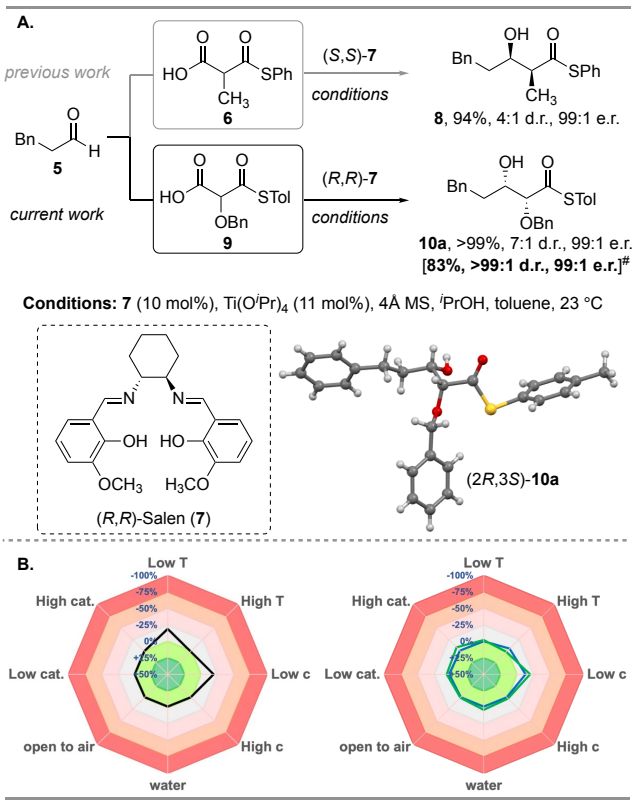


Figure 2. (**A**) A decarboxylative *syn*-propionate aldol reaction (*previous work*). A decarboxylative *syn*-glycolate aldol reaction (*this work*). #After chromatographic purification. Red, oxygen; gray, carbon; yellow, sulfur; white, hydrogen. (**B**) Sensitivity assessment of reaction yield (*left*) and stereoselectivity (*right*); enantioselectivity (blue line), diastereoselectivity (green line).

We began our studies by investigating the condensation of α-benzyloxy-MAHT **9** and hydrocinnamaldehyde **5** using our previously reported conditions (Figure 2A). The desired *syn*-diol product **10a** was obtained in quantitative yield and high diastereo- and enantio-selectivity (7:1 d.r, 99:1 e.r.). Chromatographic purification provided **10a** in 83% yield as a single stereoisomer (>99:1 d.r, 99:1 e.r.). To assess the robustness of this transformation we carried out a sensitivity screening using a modified version of the protocol described previously by the Glorious group.[23] The sensitivity of the reaction to two-fold changes in temperature, concentration, catalyst loading, or the presence of water (1 equiv.) and oxygen (open-to-air), was systematically examined (Table S1). The changes in product yield, and enantio- and diastereoselectivity of **10a** in comparison to the standard reaction conditions are illustrated using radar charts (Figure 2B). The results illustrate that this catalytic glycolate aldol is remarkably robust, and tolerates the presence of both air and water.

We next sought to explore the scope of the transformation (Figure 3). A range of branched and linear alkyl aldehydes provided the desired diol products in high yield and selectivity, including previously challenging α-branched substrates (**b** & **e**).[15] Alkyl aldehydes containing common functional groups including chloride (**f**), alkyne (**g**), alkene (**h**), and a sensitive acetal (**m**) were all tolerated. Alkynyl (**k**) and phenylacetaldehyde (**i**) were suitable substrates, although the more hindered diphenylacetaldehyde (**j**) only provided the desired product in moderate enantioselectivity. The aldol reaction with an γ-ethoxy-substituted aldehyde provided the aldol product in addition to a small quantity of the lactone **10l**. Exposure of the product mixture to *p*-toluenesulfonic acid catalyzed the quantitative conversion of the aldol product to the lactone **10l**. Importantly, α-alkoxy and β-amino aldehydes were suitable substrates, providing access to important precursors (**n** & **o** respectively) for the *de novo* synthesis of monosaccharides and iminosugars.[24–26]

The *syn*-selective glycolate aldol reaction also proved to be general for a range of structurally and electronically diverse aromatic aldehydes. Aromatic aldehydes with *meta*-, *ortho*-, and *para*-substitution gave the aldol products in excellent yield and high selectivity. A broad range of substituents were tolerated, including halides (**q** & **w**), trifluoromethyl (**s**), nitro (**p** & **v**), cyano (**r**), and reactive functionalities such as esters (**y**) and ketones (**z**). While high selectivity was observed across all substituents, electron rich aromatic aldehydes such as 2-naphthaldehyde (**u**), or 3-methoxybenzaldehyde (**x**), proved to be sluggish in the reaction, providing the diol product in moderate yield. Finally, aldehydes containing prevalent heteroaromatic scaffolds such as benzothiophene (**aa**), furan (**ab**), oxazole (**ac**), and thiazole (**ad**), were converted to the corresponding diol products in high yield and selectivity. The expected absolute and relative configurations of aliphatic diol **10e**, aromatic diol **10p**, and heteroaromatic diol **10ad** diol were confirmed by X-ray crystal analysis.

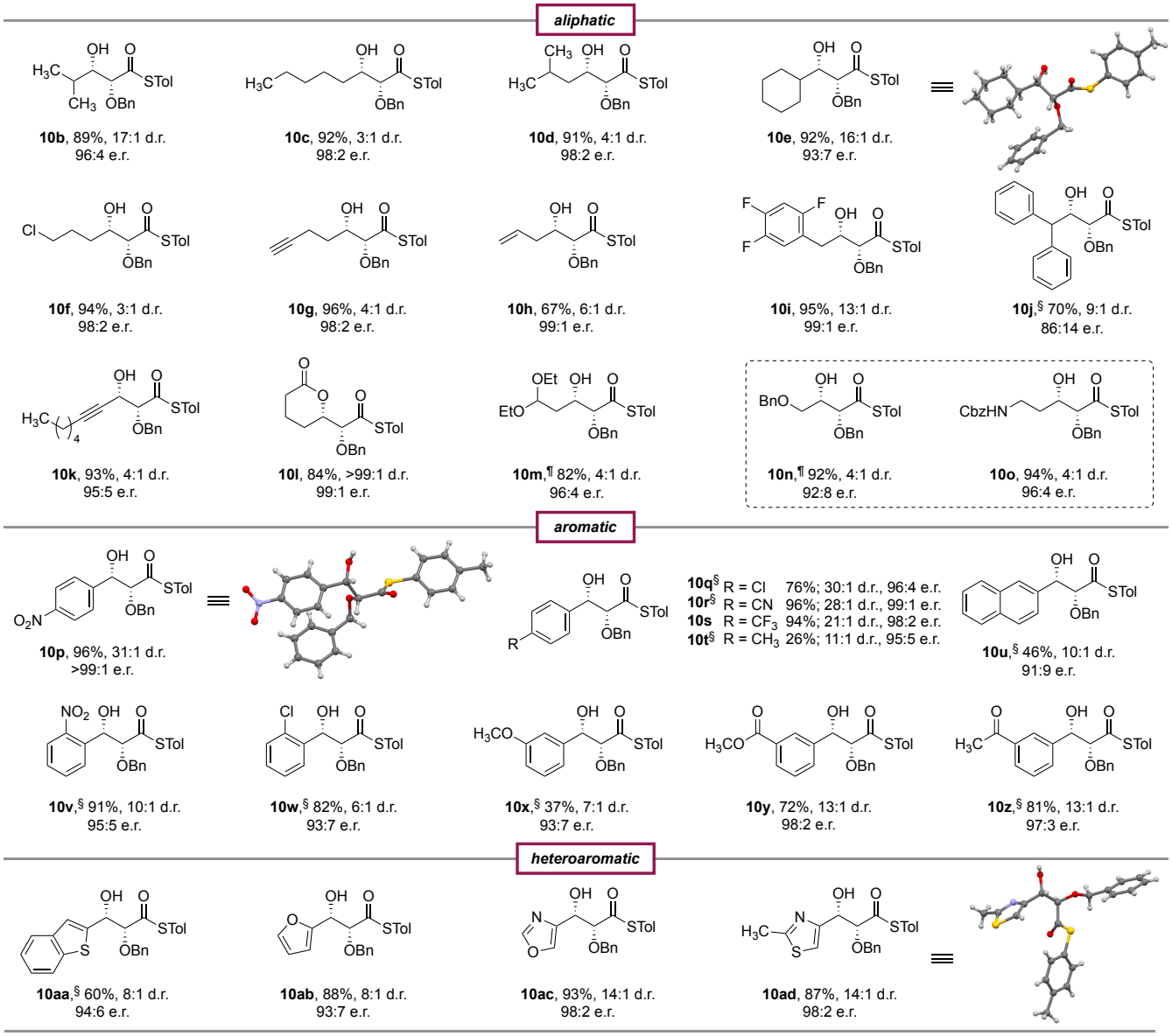


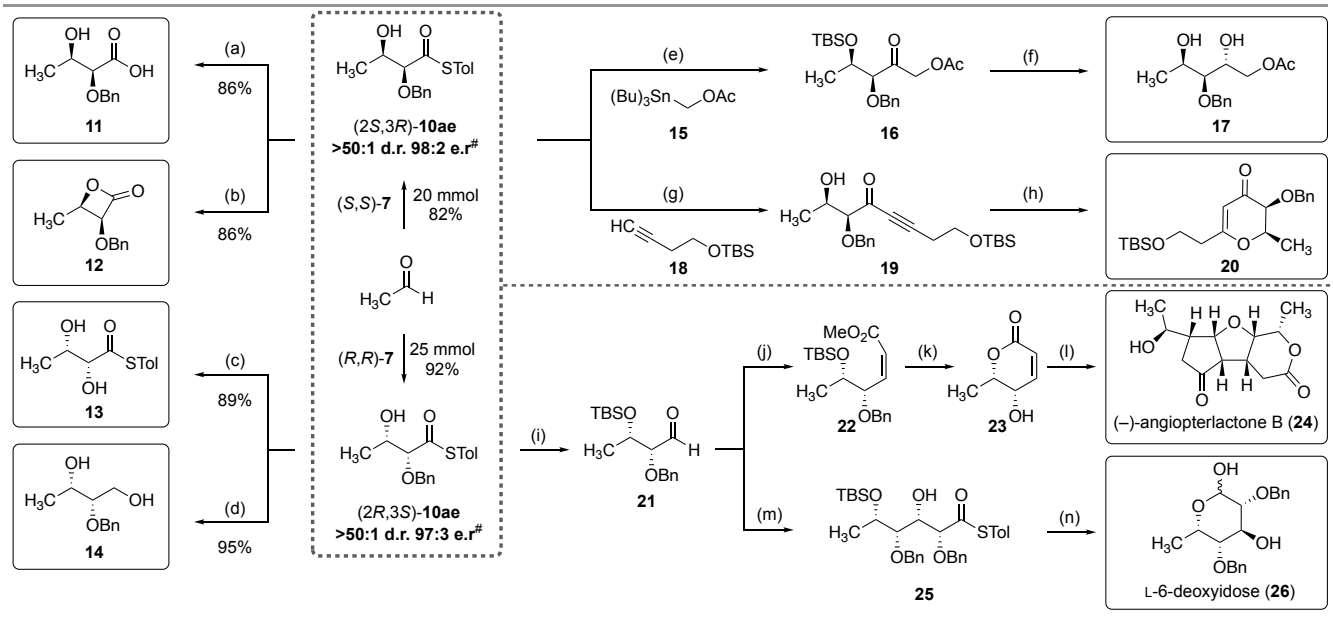
Figure 3. Aldehyde substrate scope for the *syn*-selective glycolate aldol reaction. Reactions were performed on a 0.3 mmol scale with respect to the aldehyde in toluene (0.1 M) for 24–48 hours unless otherwise stated. Isolated yields after chromatographic purification are reported. §Reaction was performed for 48 hours in toluene (0.4 M). ¶Reaction was performed using 15 mol% $Ti(O^iPr)_4$. The d.r. and e.r. values were determined by supercritical fluid chromatography (SFC) with a chiral stationary phase.

The utility of this method was further demonstrated through the synthesis of *syn*-(2*S*,3*R*)-dihydroxybutyric acid (thio)ester **10ae** and its enantiomer (2*R*,3*S*)-**10ae**, which are important building blocks for the synthesis of complex carbohydrates and other densely oxygenated natural products (Scheme 1). Prior syntheses of this valuable substrate have typically employed Sharpless dihydroxylation of the corresponding ester.[27,28] By employing our decarboxylative glycolate aldol the multigram synthesis of both enantiomers of *syn*-2,3-dihydroxybutyric acid thioester **10ae** was achieved in a single atom economic transformation. This approach avoids the olefination reaction, removes the need for toxic osmium catalysts, and is facile to run on large scale. Furthermore, the thioester provides a versatile functional handle that can be directly converted to carboxylic acid derivatives and ketones.

The enantioenriched *syn*-diol thioester products can be readily transformed into synthetically important chiral building blocks (Scheme 1). Hydrolysis of the (2*S*,3*R*)-thioester product **10ae** provided the differentially protected *syn*-(2*S*,3*R*)-dihydroxybutyric acid **11**. β-lactones serve as versatile synthetic intermediates in the synthesis of numerous important compound classes, as they undergo a variety of transformations in a stereospecific fashion.[29] The glycolate aldol products can be readily converted to α-alkoxy-β-lactones (such as **12**) by silver trifluoroacetate (AgTFA)-catalyzed intramolecular lactonization. The unprotected *syn*-(2*R*,3*S*)-dihydroxybutyric acid thioester **13** is accessed by debenzylation of (2*R*,3*S*)-**10ae** using $TiCl_4$ in

dichloromethane. Finally, reduction of (2*R*,3*S*)-**10ae** with lithium aluminium hydride ($LiAlH_4$) afforded the corresponding triol **14** in 95% yield. Importantly all of these transformations were achieved under mild reaction conditions and without loss of optical purity.

The thioester can also serve as a versatile functional handle for metal-catalyzed cross-coupling reactions to generate enantioenriched 2,3-dihydroxyketones (Scheme 1). *O*-silyl protection of the β-hydroxy group of (2*S*,3*R*)-**10ae** followed by a copper-catalyzed cross-coupling with acetoxymethyl stannane **15** yielded protected D-deoxyxylulose **16**,[30] a valuable polyoxygenated intermediate containing four orthogonal oxygen atoms that can each be selectively functionalized. *p*TsOH-mediated desilylation of **16** followed by subjection of the corresponding β-hydroxy ketone to tetramethylammonium triacetoxyborohydride [$Me_4NHB(OAc)_3$] selectively reduced it to the *anti*-diol **17**.[31] Thioester (2*S*,3*R*)-**10ae** can also be converted to the α,β-acetylenic ketone **19** via a Pd-catalyzed cross-coupling with alkyne **18**.[32] Subjection of the chiral ynone **19** to a gold-catalyzed intramolecular oxy-Michael reaction directly afforded tetrahydropyrone **20**.[33,34]



Scheme 1. Multigram scale synthesis and functionalization of both enantiomers of the thioester product **10ae**. See the Supplementary Materials for experimental details. #After chromatographic purification. (a) LiOH•H_2O (1.1 equiv), aqueous H_2O_2 (30%, 10 equiv), THF–H_2O (5:1), 23 °C, 12 h. (b) AgTFA (1.5 equiv), DIPEA (1.6 equiv), CH_2Cl_2, 24 h, 23 °C. (c) $TiCl_4$ (1.0 M in CH_2Cl_2, 2 equiv), CH_2Cl_2, 0 °C, 16 h. (d) $LiAlH_4$ (1.0 M in Et_2O, 2.2 equiv), Et_2O, 3 h, 0 °C. (e) (i) TBSOTf (1.2 equiv), DIPEA (1.5 equiv), CH_2Cl_2, 1 h, 0 °C, 94%; (ii) **15** (6 equiv), CuOAc (2 equiv), DMF, 80 °C, 24 h, 73%. (f) (i) *p*TsOH (20 mol%), CH_2Cl_2–MeOH (1:1), 6 h, 23 °C, 66%; (ii) $Me_4NHB(OAc)_3$ (28.5 equiv), CH_3CN–AcOH (1:1), –40 °C, 18 h, 69%. (g) **18** (2 equiv), CuI (2 equiv), TFP (40 mol%), $Pd(dppf)Cl_2$ (20 mol%), DIPEA (1.01 equiv), DMF, 50 °C, 48 h, 72%. (h) AuCl (5 mol%), CH_2Cl_2, 20 h, 23 °C, 74 %. (i) (i) TBSOTf (1.2 equiv), DIPEA (1.5 equiv), CH_2Cl_2, 1 h, 0 °C, 99%; (ii) $Pd(OAc)_2$ (30 mol%), $MgSO_4$ (15 equiv), Et_3SiH (10 equiv), 2 h, 0 °C, acetone, 86%. (j) $(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$ (2 equiv), NaH (2 equiv), –78 °C, 2 h, 90%. (k) (i) *p*TsOH (20 mol%), CH_2Cl_2, 23 °C, 24 h, 90%. (ii) $TiCl_4$ (1M in CH_2Cl_2, 2 equiv), CH_2Cl_2, 0 °C, 16 h, 88 %. (l) K_2CO_3 (20 mol%), DCE, 70 °C, 16 h, 16%. (m) **9** (1.2 equiv), (*R*,*R*)-**7** (10 mol%), $Ti(O^iPr)_4$ (11 mol%), ^{i}PrOH (1 equiv), toluene, 4Å MS, 23 °C, 24 h, 81%. (n) (i) CSA (20 mol%), CH_2Cl_2–MeOH (1:1), 50 °C, 20 h, 85%; (ii) DIBAL-H (1M in toluene, 2 equiv), CH_2Cl_2, –78 °C, 2 h, 83%.

O-silyl protection of the (2*R*,3*S*)-*syn* aldol product **10ae** and subsequent Pd-mediated Fukuyama reduction gave the protected dihydroxy-aldehyde **21**, a valuable intermediate in the synthesis of 6-deoxy-sugars and polyoxygenated natural products (Scheme 1). Olefination of aldehyde **21** using Still-Gennari modified Horner–Wadsworth–Emmons conditions yielded the *Z*-olefinic ester **22** in 90% yield.[35] Treatment of **22** with *p*-toluenesulfonic acid (*p*TsOH) promoted desilylation of the *O*-TBS protected β-hydroxyl group and concomitant *in situ* cyclization to the corresponding lactone. $TiCl_4$-mediated debenzylation yielded the α,β-unsaturated δ-lactone **23**. The Lawrence[36] and Bhattacharya[37] groups have previously demonstrated that lactone **23** could undergo a biomimetic dimerization in mildly basic conditions to generate (–)-angiopterlactone B (**24**) as a single diastereomer. Indeed, subjecting **23** to K_2CO_3 in 1,2-dichloroethane (DCE) provided the desired natural product in 16% yield. Finally, aldehyde **21** can be converted to stereochemically diverse deoxyhexoses via several known protocols.[24,38–40] In this case, subjection of aldehyde **21** to a second (*R*,*R*)-salen catalyzed decarboxylative glycolate aldol yielded the *syn-syn* aldol product (2*R*,3*S*,4*S*,5*S*)-**25** in 81% yield. Camphorsulfonic acid-mediated deprotection of the *O*-TBS protected alcohol initiated an intramolecular cyclization to directly yield the corresponding lactone. Partial reduction of the lactone using DIBAL-*H* afforded an

inseparable 3:1 anomeric mixture of 2,4-bis(*O*-benzyl)-L-6-deoxyidose (**26**) in 83% yield.[24]

In conclusion, we disclose a catalytic decarboxylative glycolate aldol reaction using OBn-MAHT as an activated glycolate surrogate. The mild and robust method delivers highly enantioenriched aromatic and aliphatic *syn*-diols. The α-benzyloxy-β-hydroxy thioester products serve as versatile building blocks in the stereoselective synthesis of valuable polyoxygenated molecules, as demonstrated by the multigram enantiodivergent synthesis and derivatization of dihydroxybutyric acid thioester. This method adds to the ever-growing toolbox of enantioselective decarboxylative C–C bond forming reactions using functionalized MAHTs.

ASSOCIATED CONTENT

Supporting Information

Schemes, figures, and tables; detailed experimental procedures; characterization data for all new compounds.

Accession Codes

X-ray data for compounds **10a**, **10e**, **10p**, **10r**, and **10ad** are freely available at the Cambridge Crystallographic Data Centre under deposition numbers 2371527, 2367925, 2367935, 2367938, and 2367937, respectively.

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Author Contributions

A.R.H. conceived the project and supervised the research. M.A.R., M. R., T.C., and B.B.A. performed the experiments. A.R.H. wrote the manuscript. All authors revised and approved the manuscript.

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ABBREVIATIONS

MAHT, malonic acid half thioester; MS, molecular sieves; SFC, supercritical fluid chromatography

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