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Catalytic Asymmetric Synthesis of Acyclic Arrays by Tandem 1,4-Addition-Aldol Reactions

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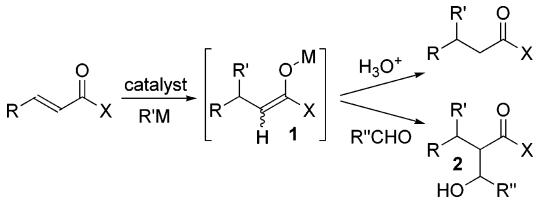
Abstract: Herein, we report efficient acyclic stereocontrol in tandem 1,4-addition-aldol reactions triggered by catalytic asymmetric organometallic addition. Grignard reagents add to α,β-unsaturated thioesters in a 1,4-fashion and the resulting magnesium enolates are trapped with aromatic or aliphatic aldehydes. The process provides a range of tandem products bearing three contiguous stereocenters with excellent control of relative and absolute stereochemistry. The various diastereomeric products have been fully characterized using single-crystal X-ray analysis and the origins of stereocontrol in this tandem protocol are discussed. The versatility and efficiency of this methodology are demonstrated in the first catalytic asymmetric synthesis of (−)-phaseolinic acid with 54% overall yield via a short and concise route.

Introduction

The generous amount of research invested into C−C bond formation via the addition of organometallic species to α,β-unsaturated carbonyl compounds now allows for this transformation to be achieved in a catalytic asymmetric manner using a range of nucleophilic and electrophilic partners (Scheme 1).[1] The initial product of reaction is the metal enolate **1** and, in the presence of a suitable carbonyl electrophile, enolate **1** can be intercepted to yield aldol type products **2** bearing up to three contiguous stereocenters. Tandem reactions attract significant research interest[2] as they can effect a rapid increase in structural and stereochemical complexity using only catalytic sources of chirality.

The reported *intra*molecular examples of catalytic asymmetric 1,4-addition-aldol reactions utilize organometallic nucleophiles in combination with substrates which contain *both* activated olefin and aldehyde functions.[3] The *inter*molecular 1,4-addition-aldol reactions described so far require the use of cyclic substrates to enforce geometrical constraints on any intermediate enolate and promote stereocontrol.[4−7] In 2001, we reported a concise synthesis of prostaglandin E_1 utilizing a tandem 1,4-addition-aldol reaction as the key transformation (A, Scheme 2).[4c] More recently, Nicolaou et al. described highly enantioselective 1,4-addition-aldol coupling using vinylzirconium nucleophiles and cyclic enones **3** (B, Scheme 2).[5] Hoveyda et al. have achieved highly enantio- and diastereoselective 1,4-addition-aldol coupling using organozinc reagents and chromenones **6** (C, Scheme 2).[6] Hayashi et al. used a chiral rhodium catalyst to achieve an intermolecular 1,4-addition-aldol reaction involving an organoboron addition to an α,β-unsaturated ketone.[7] The racemic version of the reaction proceeded smoothly with excellent control of relative stereochemistry. Attempts to control the absolute stereochemistry of the reaction using chiral ligands gave high enantioselectivity but the chemical yield and

Scheme 1. Catalytic Tandem 1,4-Addition-Aldol Reactions



(1) For reviews, see: (a) Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 5560−5562. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171−196; (c) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. in *Modern Organocopper Chemistry*; Krause, N., Ed.; VCH: Weinheim, Germany, 2002, pp 224−258. (d) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346−353. (e) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221−3236. (f) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis;* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999, Vol. 3, pp 1105−1120. (g) Yamasaki, K.; Hayashi, T. *Chem. Rev.* **2003**, *103*, 2829−2844.

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(5) Nicolaou, K. C.; Tang, W.; Dagneau, P.; Faraoni, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 3874−3879. Control of the relative stereochemistry proved challenging but this was not of great importance as two of the three new stereogenic centers were removed via dehydration to reform the α,β-unsaturated system.

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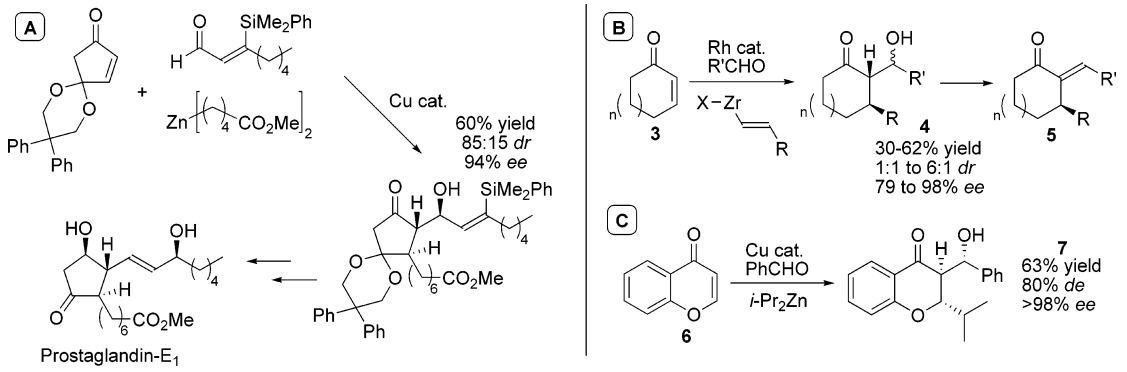
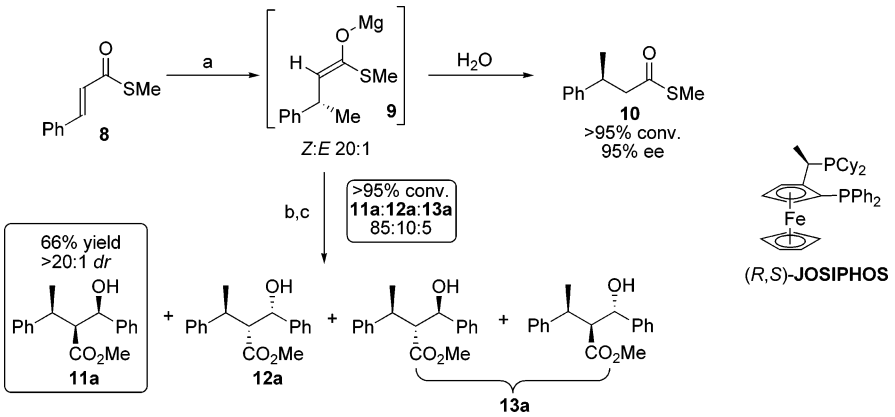
Scheme 2. Applications of Tandem 1,4-Addition-Aldol Coupling



Scheme 3. Tandem 1,4-Addition-Aldol Coupling of Thioester Substrates



(a) $CuBr \cdot SMe_2$ (0.05 equiv), (*R*,*S*)-JOSIPHOS (0.06 equiv), MeMgBr (1.2 equiv), TBME, −75 °C, 16 h; (b) PhCHO (2 equiv), −75 °C, 1 min; (c) K_2CO_3, MeOH, room temperature, 3 h.

diastereoselectivity were limited. To the best of our knowledge, this is the only acyclic example of a catalytic asymmetric, intermolecular 1,4-addition-aldol coupling via organometallic addition. On the basis of the notion that acyclic stereocontrol via catalytic asymmetric tandem 1,4-addition-aldol coupling remains a major challenge and that the products of such transformations are particularly valuable for natural product synthesis, we wished to develop a method to achieve this goal.

Recently, we have developed a number of protocols for the catalytic asymmetric 1,4-addition of Grignard nucleophiles to α,β-unsaturated carbonyl compounds.[8] We have found α,β-unsaturated thioester substrates to be of great utility; a wide range of alkyl and aryl groups are tolerated at the termini of the olefinic bond and various Grignard species can be added with high yield and enantioselectivity. We envisioned that this methodology might be utilized to achieve 1,4-addition-aldol reactions on the basis of the premise that magnesium enolates have been shown to display high reactivity toward aldol coupling,[9] and furthermore sulfur containing enolates have been successfully employed in a range of diastereoselective aldol reactions.[10] Accordingly, we have developed a powerful and efficient protocol for the catalytic asymmetric construction of acyclic stereochemical triads using α,β-unsaturated thioester substrates, methyl Grignard nucleophiles, and aromatic or aliphatic aldehydes. The tandem reaction products are formed in good yield with excellent control of relative and absolute stereochemistry across the three newly formed stereogenic centers. We also demonstrate the utility and efficiency of this new methodology by achieving the first catalytic asymmetric synthesis of (−)-phaseolinic acid using a short and concise route.

Results and Discussion

Our initial hypothesis was that the diastereoselectivity of the aldol coupling ought to be strongly influenced by the steric properties of the substituents at the γ-position of the intermediate enolate **9** (Scheme 3). With this in mind, we elected to use thioester **8** in conjunction with a methyl Grignard nucleophile in order to explore the potential for tandem 1,4-addition-aldol reactions. Thus, the intermediate enolate **9** will feature (in relative terms) "large" (Ph, "*A*" value = 3.0 kcal)[11] and "small" (Me, "*A*" value = 1.7 kcal) substituents at the γ-position. This steric discrepancy ought to provide the best opportunity for diastereoselective attack on the carbonyl electrophile in the aldol coupling step.

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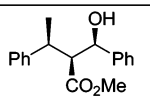
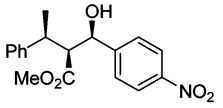
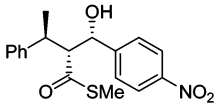
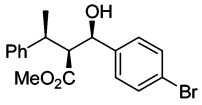
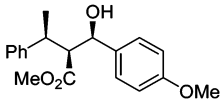
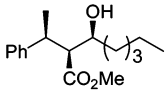
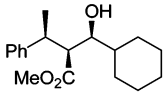
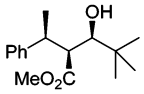
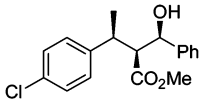
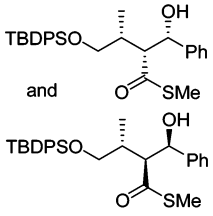
Table 1. Substrate Screening for Tandem 1,4-Addition-Aldol Coupling

Entry	Ester	R'CHO	*conv.* [a]	11:12:13 [a]	*ee* [b]	Final Product [c]	
1	**8**	R'=Ph	>95%	85:10:5	95%	**11a** [d] 66% >20:1 *dr*	
2	**8**	R'=4-NO_2-C_6H_4	>95%	80:15:5	95%	**11b** 62% >20:1 *dr*	
						12b [d,e] 6% >20:1 *dr*	
3	**8**	R'=4-Br-C_6H_4	>95%	80:15:5	95%	**11c** [f] 68% >20:1 *dr*	
4	**8**	R'=4-OMe-C_6H_4	>95%	80:15:5	95%	**11d** [f] 54% >20:1 *dr*	
5	**8**	R'=*n*-pent	>95%	90:5:5	95%	**11e** [g] 74% >20:1 *dr*	
6	**8**	R'=*c*-hex	>95%	>95:<5:0	95%	**11f** [f] 76% >20:1 *dr*	
7	**8**	R'=*t*-Bu	>95%	>95:<5:0	95%	**11g** [f] 73% >20:1 *dr*	
8	**18**	R'=Ph	>95%	80:15:5	>99%	**11h** [f] 49% >20:1 *dr*	
9	**19**	R'=Ph	>95%	~50:50:0	98%	**11j/12j** [h] 49% ~1:1 *dr*	

[a] Determined by ^{1}H NMR. [b] Measured by HPLC/GC of corresponding 1,4-addition product (**10**, **20,** or **21**) prior to aldol coupling. [c] Isolated yield after chromatography and/or crystallization. [d] Stereochemistry assigned via single-crystal X-ray analysis. [e] Compound **12b** was isolated as the thioester to allow for determination of absolute stereochemistry by X-ray analysis employing heavy atom effect. [f] Stereochemistry assigned by comparison to products **11a** and **11e**. [g] Stereochemistry assigned via subsequent derivatization. [h] Absolute configuration assigned via subsequent derivatization studies; relative configuration assigned by comparison to compounds **11a** and **11e**; diastereomers separated as thioesters (without methanolysis) by chromatography.

The initial 1,4-addition proceeded smoothly using the Cu/JOSIPHOS catalyst we have utilized previously[8d] and it was quickly found that the intermediate magnesium enolate **9** readily underwent aldol coupling with benzaldehyde, with complete conversion after 1 min at −75 °C. This is in direct contrast to the extended reaction times we have found necessary for aldol coupling of the corresponding zinc enolates.[4] This sequence provides products with three contiguous stereocenters and, while four diastereomeric aldol products (**11**−**13**) are possible, we observed a ratio of 85:10:5 (**11a**/**12a**/**13a**) by ^{1}H NMR. Attempts

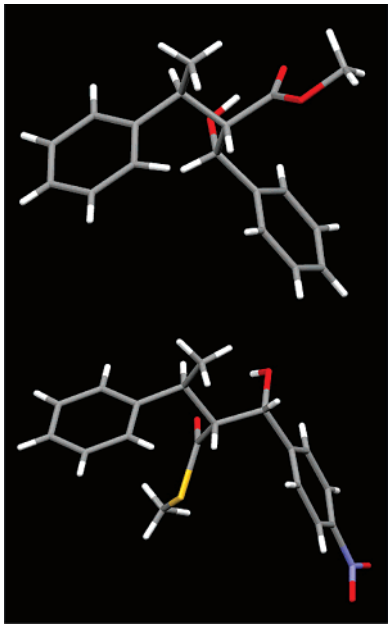


Figure 1. Crystal structure representations of **11a** (top) and **12b** (bottom).

to increase the diastereoselectivity further by varying solvent, substrate addition order/addition time and quenching conditions were ineffective. The observed level of stereocontrol with this acyclic substrate is comparable to that obtained by Hoveyda et al. using cyclic chromenone substrates.[6] We found that the crude aldol product could be easily converted to the corresponding oxygen ester affording higher stability to chromatography and, crucially, allowing the diastereomeric aldol products to be readily separated by crystallization. We were able to isolate the major diastereomer **11a** as a single compound in 64% yield.

Determination and Origin of Stereochemistry. The enantiomeric excess (95% ee) of the tandem 1,4-addition-aldol reaction above was determined by HPLC analysis of the 1,4-addition product **10** prior to aldol coupling. While we were unable to isolate the second diastereomer **12a**, we could isolate a pure sample of the corresponding diastereomer from a subsequent, analogous reaction (thioester **12b**, Scheme 5, Table 1, entry 2). With pure, crystalline samples of the first (**11a**) and second (**12b**) diastereomers in hand, we were able to assign relative (**11a**) and absolute (**12b**, using sulfur as a "heavy atom") configurations using single-crystal X-ray analysis. Crystal structure representations can be seen in Figure 1. Since all of the diastereomeric products discussed thus far are formed from the same enantio-enriched enolate **9**, both **11a** and **12b** must possess like configuration (3*S*) at the benzylic stereocenter. On the basis of this observation and our crystal structure analyses, we have assigned the first diastereomer as (2*S*,3*S*,1′*R*)-**11a** and the second diastereomer as (2*R*,3*S*,1′*S*)-**12a**. The assignment of (2*S*,3*S*,1′*R*) for the major diastereomeric product was confirmed in subsequent studies where an analogous major product **11e** (Scheme 5, Table 1, entry 5) was derivatized to natural (−)-phaseolinic acid (2*S*,3*S*,4*S*)-**22** (vide infra, Scheme 6).

The second step in the process outlined in Scheme 3 is, in essence, a diastereoselective aldol reaction using a chiral nucleophile (enolate) and a prochiral electrophile (aldehyde). Numerous studies have been made concerning stereochemistry in the direct aldol reaction[12] and accordingly, a chair like Zimmerman−Traxler transition state model (Scheme 4) would seem pertinent for this magnesium mediated aldol reaction. It would also seem logical that (1) both enolate and aldehyde are monodentate ligands; (2) the large phenyl substituent on the aldehyde occupies a pseudoequatorial site to minimize unfavorable diaxial interactions. The observed ratio of *syn*- (**11a** + **12a**) to *anti*- (**13a**) aldol products is high (≥20:1 by ^{1}H NMR), and it can be seen from Scheme 4 that if high energy boat conformations are ignored, only the *Z*-enolate **14** can give rise to the observed *syn*-aldol products **11a** and **12a**. This indicates that the initial 1,4-addition reaction furnishes the magnesium enolate **9** with high *Z*-selectivity. To investigate this hypothesis further, we attempted to isolate the intermediate enolate **9** (Scheme 4) as the corresponding trimethylsilyl thioketene acetal **9a** directly from the 1,4-addition reaction mixture. This proved unsuccessful and we were unable to detect silylated products under these conditions.[13] However, treatment of 1,4-addition product **10** (Scheme 4) with lithium diisopropylamide and trimethylsilyl chloride afforded the thioketene acetal **9a** with high *Z*/*E* selectivity (88:12 by ^{1}H NMR). Enolate geometry was assigned based on the observed "weak" NOE interaction (Scheme 4) in the major enolate product (*Z*) and a much more (∼15 times) intense interaction in the minor enolate product (*E*). Reaction between lithium enolate **9** and PhCHO generated the *syn*-aldol product with high diastereoselectivity. These observations indicate that our tandem reaction (Scheme 3) and the lithium mediated aldol reaction (Scheme 4) proceed via the same enolate intermediate **9** with a high preponderance of the *Z*-geometry.

To rationalize the selectivity observed between the two *syn*-aldol products **11a** and **12a**, we might consider two more detailed transition state models (Figure 2). Minimization of the $A_{1,3}$-strain (**16**) in the enolate would promote *Re*-facial attack on the enolate, as the phenyl substituent is more sterically demanding than the methyl group. This transition state would predict the anti,syn diastereomer **12a** to be the major product. This is in direct disagreement with our findings and is therefore disregarded. Alternatively, minimization of the inherent *syn*-pentane interaction (**17**)[12a,c] in the transition state would promote *Si*-facial attack on the enolate giving rise to *syn*,*syn*-**11a** as the major diastereomer. This is supported by our findings, and we would suggest **17** to be a likely transition state model for this reaction. This analysis would suggest that the high level of diastereoselectivity is reliant on the steric differential between the two groups (Ph and Me) at the γ-stereogenic center present in the intermediate enolate.

Scope and Applications. To further probe this mechanism for stereocontrol and to investigate the scope of the reaction we screened other thioester and carbonyl partners (Scheme 5, Table 1). Substrate **8** reacted smoothly and in a stereoselective manner with aromatic and aliphatic aldehydes displaying excellent conversions in all cases. Diastereoselectivity was

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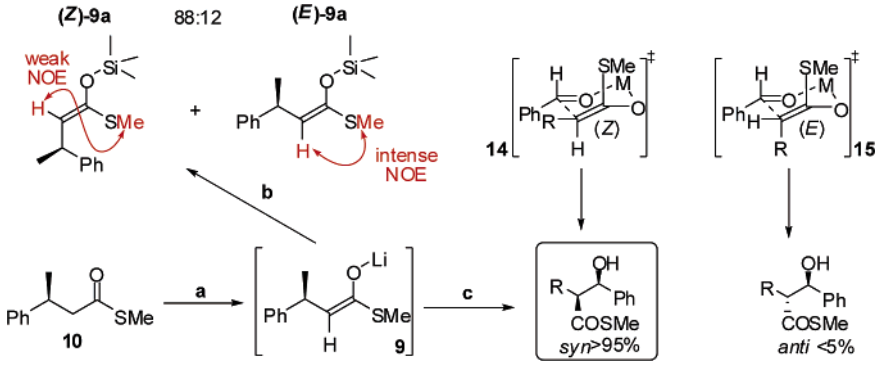
(13) It is likely that the presence of stoichiometric amounts of magnesium(II) halides either precludes the silylation of enolate **9** or causes degradation of the desired product **9a**.

Scheme 4. Enolate Selectivity



(a) Diisopropylamine (1.1 equiv), *n*-BuLi (1.1 equiv), TBME, −50 °C, 2 h; (b) trimethylsilyl chloride (1.1 equiv), −50 °C to room temperature, 1 h; (c) PhCHO (2 equiv), −75 °C to room temperature, 1 h.

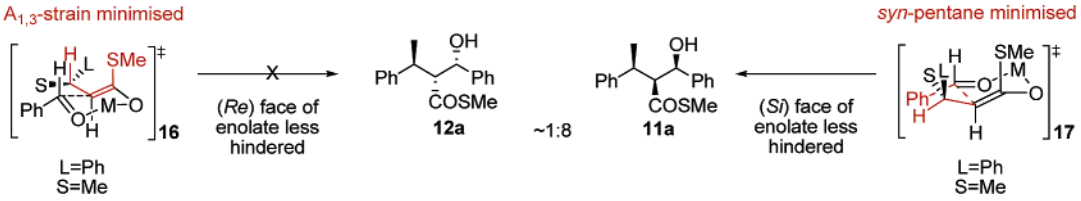
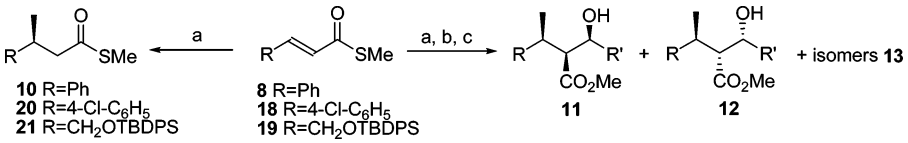


Figure 2. Model for anti,syn/syn,syn selectivity.

Scheme 5. Substrate Screening



(a) CuBr·SMe_2 (0.05 equiv), JOSIPHOS (0.06 equiv), MeMgBr (1.2 equiv), TBME, −75°, 16 h; (b) R′CHO (2 equiv), −75°, 1 min; (c) K_2CO_3, MeOH, room temperature, 3 h.

typically high for the aromatic aldehydes (entries 1−4) and very high for the aliphatic aldehydes (entries 5−7). Removal of the minor diastereomeric products was readily achieved in all cases by column chromatography and/or crystallization. Diastereomerically pure products **11a**−**h** (with ≥95% ee) were obtained in moderate to good overall yields based on the starting thioester substrates. Aryl substituted thioester **18** yielded similar results to **8** (entry 8), while substrate **19** (entry 9), bearing a protected hydroxy function, reacted smoothly but in a nondiastereoselective manner. While we were able to separate the two diastereomeric products **11j**/**12j**, the stereochemical assignment (syn,syn or syn,anti) based on NMR data was not successful. As we proposed earlier, the diastereoselectivity of this reaction is likely controlled by the steric differential between the two substituents at the γ-position in the intermediate enolate. Considering substrate **19**, the two γ-substituents are methyl (*A* value = 1.7 kcal) and CH_2OTBDMS (*A* value ≈ 1.8 kcal).[11] These two groups have almost equivalent steric parameters and so the lack of diastereoselectivity in the ensuing aldol reaction is, perhaps, not surprising.

The products **11a**−**j** show how this tandem methodology can be used to create structurally complex, acyclic stereochemical triads both rapidly and efficiently. In the majority of cases above, a phenyl group appears to serve as a "bulky" substituent at the γ-position of the enolate to promote diastereoselectivity in the ensuing aldol transformation. We were hopeful that this phenyl function might be utilized as a synthetic handle for further transformations via exhaustive oxidation to the corresponding carboxylic acid. This would greatly expand the scope of our tandem 1,4-addition-aldol methodology and allow access to important families of biologically active products (Scheme 6). The three natural products shown below belong to the paraconic acid family[14] and have been isolated from various lichens, mosses, and fungi. These compounds, displaying useful antifungal, antitumor, and antibacterial properties, have attracted significant interest from the synthetic-organic community.[15] The three specific paraconic acids shown below each display trans−cis stereochemistry and are often described as the most challenging of the paraconic acids from a synthetic viewpoint.[15e] Using our tandem 1,4-addition-aldol pathway, we might provide access to the paraconic acid skeleton in as little as four synthetic transformations, with the sequence relying on a key oxidation of the aromatic ring.

With the simplest pentyl-substituted paraconic acid (phaseolinic acid **22**)[15] as our target, the tandem product **11e** was synthesized as a single diastereomer in 72% yield and 95% ee (Table 1, entry 5) using our 1,4-addition-aldol methodology with

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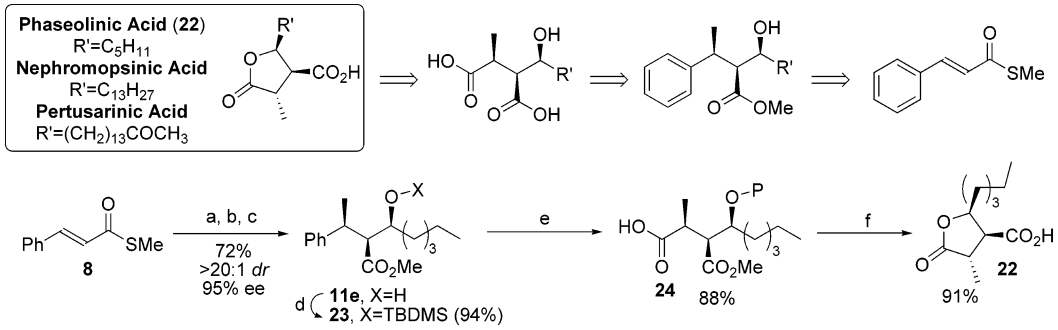
(15) For isolation and asymmetric syntheses, see (a) Mahato, S. B.; Siddiqui, K. A. I.; Bhattacharya, G.; Ghosal, T.; Miyahara, K.; Sholichin, M.; Kawasaki, T. *J. Nat. Prod.* **1987**, *50*, 245−247. (b) Jacobi, P. A.; Herradura, P. *Tetrahedron Lett.* **1996**, *37*, 8297−8930. (c) Drioli, S.; Felluga, F.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *J. Org. Chem.* **1998**, *63*, 2385−2388. (d) Ariza, X.; Garcia, J.; Lopez, M.; Montserrat, L. *Synlett* **2001**, 120−122. (e) Brecht-Forster, A.; Fitremann, J.; Renaud, P. *Helv. Chim. Acta* **2002**, *85*, 3965−3974. (f) Zhang, Z.; Xiyan, L. *Tetrahedron: Asymmetry* **1996**, *7*, 1923−1928. (g) Amador, M.; Ariza, X.; Garcia, J.; Ortiz, J. *J. Org. Chem.* **2004**, *69*, 8172−8175.

Scheme 6. Catalytic Asymmetric Synthesis of Phaseolinic Acid



(a) $CuBr{\cdot}SMe_2$ (0.05 equiv), JOSIPHOS (0.06 equiv), MeMgBr (1.2 equiv), TBME, −75°, 16 h; (b) PhCHO (2 equiv), −75°, 1 min; (c) K_2CO_3, MeOH, room temperature, 3 h; (d) TBDMSOTf (1.20 equiv), 2,6-lutidine (1.20 equiv), THF, room temperature, 3 h; (e) $RuCl_3$ (0.10 equiv), $NaIO_4$ (50 equiv), $MeCN/EtOAc/H_2O$, room temperature, 16 h; (f) HBr (48%), reflux, 3 h.

hexanal as the carbonyl component. With the ensuing aromatic oxidation in mind, we elected to protect the free hydroxyl function in **11e**. Coupling of the secondary alcohol with *tert*-butyldimethylsilyl triflate proceeded efficiently affording compound **23** which was used to test exhaustive oxidation of the aromatic system. We desired a pH-neutral procedure for oxidation to avoid any potential epimerisation or desilylation and inspection of the literature revealed a simple procedure using catalytic $RuCl_3$ and $NaIO_4$ as the stoichiometric oxidant.[16] In our hands this method could be used without any modification, and we were able to isolate the carboxylic acid **24** in high yield without any loss of stereochemical integrity (^{1}H NMR). The remaining synthetic transformations included ester hydrolysis, alcohol deprotection, and lactonization. We postulated that these three transformations might be effected simultaneously under acidic conditions. Exposure of **24** to 1 M HCl in THF yielded only starting material after 16 h, indicating that more vigorous conditions were required. Refluxing compound **24** in aqueous (48%) HBr for 3 h resulted in clean alcohol deprotection, ester hydrolysis, and lactonization to give the desired phaseolinic acid **22** in 91% yield after chromatography. The physical (melting point, optical rotation) and spectroscopic (^{1}H and ^{13}C NMR) data were in agreement with literature values.[14] On the basis of our assignment of the absolute stereochemistry for the tandem product **11e**, we can confirm the revised stereochemistry for (−)-phaseolinic acid [(2*S*,3*S*,4*S*)-**22**] reported by Drioli et al. in 1998.[15c] Our concise, catalytic asymmetric synthesis of phaseolinic acid was achieved with an overall yield of 54%. The route, while short and efficient, is also the first to employ a catalytic asymmetric approach. Moreover, it is a clear demonstration of the potential and efficiency of the tandem 1,4-addition-aldol methodology described here.

Summary

We have developed the first catalytic asymmetric protocol for acyclic 1,4-addition-aldol coupling using organometallic nucleophiles. Using α,β-unsaturated thioesters and methyl Grignard reagents, the chemical yields and levels of stereocontrol displayed in the tandem products are comparable to recent reports using cyclic systems and are well in excess of any reported results for acyclic systems. The utility of this tandem protocol is exemplified by the first catalytic asymmetric synthesis of phaseolinic acid, accomplished with an overall yield of 54%, via an exceptionally short and efficient route.

(16) Nunez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 1928−1932.

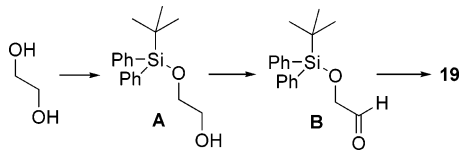
Experimental Section

General. ^{1}H NMR spectra were recorded at 400 or 500 MHz with $CDCl_3$ (referenced to 7.26 ppm) as solvent. ^{13}C NMR spectra were recorded at 100 or 125 MHz with $CDCl_3$ (referenced to 77.1 ppm) as solvent. Coupling constants (*J*) are given in Hz. Varian Gemini 200, VXR300, AMX400 and Inova 500 spectrometers were used throughout. HRMS data were obtained using a JEOL JMS-600H spectrometer. A Shimadzu 10A system was used for HPLC and Hewlett-Packard HP6890 for GC analysis. Optical rotations were measured at 254 μm using a Schmidt & Haendsch polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL and measurements are given in 10^{-1} deg cm^2 g^{-1}). Thin-layer chromatography was performed on commercial Kieselgel $60F_{254}$ silica gel plates; $KMnO_4$ and $H_3[P(Mo_3O_{10})_4]{\cdot}H_2O$ were used for visualization. Flash chromatography was performed using silica gel. Reagents were obtained from Sigma Aldrich Chemie BV, solvents were purified according to standard methods, and the JOSIPHOS ligand was obtained as a gift from Solvias (Basel).

Synthesis of Thioester Substrates. 3-Phenyl-thioacrylic Acid *S*-Methyl Ester (8). $AlCl_3$ (6 g, 45 mmol) and $Me_3Si-SMe$ (6.78 mL, 48 mmol) were added to a stirred solution of methyl *trans*-cinnamate (6 g, 36.9 mmol) in dry THF (100 mL) under a nitrogen atmosphere at room temperature. The reaction mixture was heated to reflux for 4 h and subsequently quenched at room temperature by the addition of aqueous phosphate buffer (pH 7). The mixture was partitioned between Et_2O (50 mL) and water, and the aqueous layer extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and filtered, and the solvent was evaporated. Flash chromatography of the yellow residue over silica gel, using pentane-Et_2O (50:1) gave title compound **8** (6.0 g, 91%) as a clear oil that crystallized upon standing: mp 49.2−50.1 °C. ^{1}H NMR δ 7.62 (1H, d, J = 15.8 Hz): 7.56−7.50 (2H, m), 7.40 (3H, dd, J = 6.4, 3.6 Hz), 6.74 (1H, d, J = 15.8 Hz), 2.43 (3H, s). ^{13}C NMR: δ 189.9, 140.0, 133.9, 130.3, 128.7, 128.2, 124.6, 11.5. HRMS: calcd for $C_{10}H_{10}OS$, 178.04523; found, 178.04589.

3-(4-Chloro-phenyl)-thioacrylic Acid *S*-Methyl Ester (18). $AlCl_3$ (1.63 g, 12.20 mmol) and $Me_3Si-SMe$ (1.87 mL, 13.22 mmol) were added to a stirred solution of (*E*)-methyl 3-(4-chlorophenyl)acrylate (2.0 g, 10.17 mmol) in dry THF (40 mL) under a nitrogen atmosphere at room temperature. The reaction mixture was heated to reflux for 90 min. The reaction mixture was then quenched at room temperature by the addition of aqueous phosphate buffer (pH 7). The mixture was partitioned between Et_2O (20 mL) and water, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and filtered, and the solvent was evaporated. Triturating the yellow residue with cold pentane gave title compound **18** (1.90 g, 88%) as opaque white needles: mp 99.7−100.1 °C. ^{1}H NMR: δ 7.56 (1H, d, J = 15.8 Hz), 7.50−7.45 (2H, m), 7.39−7.34 (2H, m), 6.70 (1H, d, J = 15.8 Hz),

2.43 (3H, s). ^{13}C NMR: δ 189.8, 138.5, 136.3, 132.5, 129.4, 129.1, 125.1, 11.6. HRMS: calcd for $C_{10}H_9ClOS$, 212.00626; found, 212.00547.



4-(*tert*-Butyl-diphenyl-silanyloxy)-but-2-enethioic Acid *S*-Methyl Ester (19). *tert*-Butyl-chlorodiphenylsilane (10 mL, 38.5 mmol) was added to a stirred solution of ethane-1,2-diol (12 mL, 231 mmol) and imidazole (2.88 g, 42.4 mmol) in THF (200 mL) under nitrogen atmosphere. The resulting mixture was stirred for 24 h at room temperature and quenched with 200 mL water followed by the addition of 200 mL Et_2O. After phase separation and extraction of the aqueous phase with Et_2O (3 × 200 mL), the combined organic phases were dried ($MgSO_4$), concentrated, and purified by flash chromatography (eluent pentane/EtOAc 4:1) to afford monosilyl alcohol **A** as a colorless oil (9.140 g, 79% yield). A solution of **A** (9.14 g, 30.5 mmol) and IBX (11.09 g, 39.6 mmol) in EtOAc (200 mL) was refluxed for 24 h and cooled to room temperature. The IBX and benzoic acid were removed via filtration (Celite pad) and washed with EtOAc. The filtrate was concentrated under reduced pressure to give aldehyde **B**, which was used in the next step without any purification (8.81 g, 97% yield). A solution of aldehyde **B** (8.81 g, 29.6 mmol) and $Ph_3PCHCOSEt$ (13.99 g, 38.4 mmol) in CH_2Cl_2 (150 mL) was refluxed for 24 h. The solution was concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 40:1) to afford title compound **19** as a colorless oil (9.08 g, 80% yield). ^{1}H NMR: δ 7.67 (4H, dd, J = 7.60, 1.20 Hz), 7.42 (6H, m), 6.90 (1H, dt, J = 15.20, 3.20 Hz), 6.55 (1H, dt, J = 14.80, 2.40 Hz), 4.35 (2H, m), 2.98 (2H, q, J = 7.60 Hz), 1.31 (3H, t, J = 7.20 Hz), 1.09 (9H, s). ^{13}C NMR: 190.1, 142.7, 135.4, 132.9, 129.9, 127.8, 126.7, 62.8, 26.7, 23.2, 19.2, 14.8. MS (EI): 327 (71%, M^+ − *tert*-butyl), 384 (100%, M^+).

Protocol for Tandem 1,4-Addition-Aldol Coupling. General Procedure A. A Schlenk flask fitted with a magnetic stirrer was flame-dried under vacuum and cooled before CuBr·SMe_2 (4.8 mg, 0.04 equiv) and JOSIPHOS (16.4 mg, 0.05 equiv) were added. A triple evacuation-N_2 purge was carried out and TBME (2.5 mL) was added. Stirring at room temperature for 15 min gave an orange solution which was cooled to −75 °C. A 3 M solution of MeMgBr in Et_2O (0.20 mL, 1.20 equiv) was added dropwise over 2 min to give a yellow solution. The thioester substrate (0.50 mmol, 1.00 equiv) was dissolved in TBME (1 mL) and added to the reaction flask at −75 °C over 2 min. The mixture was left to stir for 16 h then warmed to room temperature over 30 min. A sample of the mixture was removed and passed through a short silica plug using hexane/TBME (5:1) as eluent to provide a purified sample of the 1,4-addition product (**10**, **20**, or **21**) for chiral HPLC analysis. The reaction flask was recooled to −75 °C before dropwise addition of the aldehyde (1.00 mmol, 2.00 equiv) over 2 min. A 2:1 mixture of THF/H_2O (2 mL) was added, and the mixture was warmed to room temperature over 30 min. Saturated NH_4Cl (aq, 5 mL) was added, and the mixture was stirred for 30 min. After addition of Et_2O (10 mL), the aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The combined organic phases were washed (brine) and dried ($MgSO_4$), and the solvent was evaporated to give an orange oil. This was dissolved in MeOH (10 mL), and K_2CO_3 (1 g) was added before stirring at room temperature for 3 h. After addition of Et_2O (10 mL) and aqueous 1 M HCl (to ∼ pH 1), the aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The combined organic phases were washed (brine) and dried ($MgSO_4$), and the solvent was evaporated to give an orange oil. Flash column chromatography (10:1 hexane/EtOAc) afforded the purified tandem 1,4-addition-aldol product as a mixture of diastereomers. Crystallization (i-Pr_2O) afforded the purified product as a single diastereomer.

(3*S*)-3-Phenyl-thiobutyric Acid *S*-Methyl Ester (10). The compound was used to determine enantiomeric excess of tandem 1,4-addition-aldol reactions using thioester **8** as substrate (products **11a**−**g**). It was prepared using general procedure A and isolated from a sample of the reaction mixture prior to aldehyde addition (aldol coupling). Title compound **10** was obtained as a clear oil: $[\alpha]_D$ = +45.1 (*c* 0.27, $CHCl_3$). ^{1}H NMR: δ 7.35−7.17 (5H, m), 3.43−3.29 (1H, m), 2.84 (2H, dq, J = 14.8, 7.4 Hz), 2.27 (3H, s), 1.31 (3H, d, J = 6.9 Hz). ^{13}C NMR: δ 198.6, 145.3, 128.4, 126.7, 126.4, 52.0, 36.9, 21.4, 11.5. HRMS: calcd for $C_{11}H_{14}OS$, 194.07653; found, 194.07651. HPLC analysis indicated an enantiomeric excess of 97% [Chiralcel OD-H column; flow, 0.5 mL/min; heptane/*i*-PrOH, 99:1, 210 nm; minor enantiomer (−)-**10**, t_R = 10.76 min; major enantiomer (+)-**10**, t_R = 12.08 min].

(2*S*,3*S*,1′*R*)-2-(Hydroxy-phenyl-methyl)-3-phenyl-butyric Acid Methyl Ester (11a). The compound was obtained using general procedure A from thioester **8** (0.50 mmol, 90 mg) and benzaldehyde (1.00 mmol, 106 mg). After purification, title compound **11a** was isolated as a white solid (94 mg, 66%, >20:1 dr, 95% ee based on analysis of 1,4-addition product **10** prior to aldol coupling): mp 133.5−134.5 °C; $[\alpha]_D$ +5.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ ppm 7.43−7.08 (10 H, m), 4.45 (1 H, dd, J = 9.49, 3.44 Hz), 3.69 (1 H, d, J = 9.55 Hz), 3.53 (3 H, s), 3.42−3.32 (1 H, m), 2.93 (1 H, dd, J = 10.58, 3.46 Hz), 1.28 (3 H, d, J = 7.04 Hz). ^{13}C NMR: δ ppm 175.5, 144.0, 142.8, 129.0, 128.5, 127.7, 127.5, 127.1, 125.3, 72.2, 59.7, 51.8, 39.7, 20.3. HRMS: calcd for $C_{18}H_{20}O_3Na$ ($M + Na^+$), 307.1304; found, 307.1297.

(2*S*,3*S*,1′*R*)-2-[(4-Nitro-phenyl)-hydroxy-methyl]-3-phenyl-butyric Acid Methyl Ester (11b). Compound **11b** was obtained using general procedure A from thioester **8** (0.50 mmol, 90 mg) and 4-nitrobenzaldehyde (1.00 mmol, 151 mg). After purification, title compound **11b** was isolated as a white solid (102 mg, 62%, >20:1 dr, 95% ee based on analysis of 1,4-addition product **10** prior to aldol coupling): mp 150.5−151.5 °C; $[\alpha]_D$ −26.4 (*c* 0.8, $CHCl_3$). ^{1}H NMR: δ ppm 8.16 (2 H, dd, J = 8.78, 2.37 Hz), 7.62−7.16 (7 H, m), 4.51 (1 H, d, J = 9.75 Hz), 4.05 (1 H, dd, J = 9.76, 2.42 Hz), 3.76−3.31 (4 H, m), 2.94 (1 H, td, J = 11.07, 2.62 Hz), 1.32 (3 H, d, J = 9.44 Hz). ^{13}C NMR: δ ppm 175.0, 150.3, 147.2, 143.1, 129.0, 127.4, 127.2, 126.0, 123.5, 71.4, 59.0, 51.9, 39.7, 20.4. HRMS calcd for $C_{18}H_{19}NO_5Na$ ($M + Na^+$), 352.1155; found, 352.1109.

(2*R*,3*S*,1′*S*)-2-[Hydroxy-(4-nitro-phenyl)-methyl]-3-phenyl-thiobutyric Acid *S*-Methyl Ester (12b). Compound **12b** was obtained as the second (minor) diastereomer from the synthesis of compound **11b** (see above) using general procedure A, and was crystallized preferentially (i-Pr_2O) from the reaction mixture prior to methanolysis. It was obtained as clear needles (6%) suitable for single-crystal X-ray analysis. ^{1}H NMR: δ ppm 8.21 (2H, d, J = 8.71 Hz), 7.52−7.43 (3H, m), 7.34−7.26 (2H, m), 7.26−7.17 (2H, m), 5.23 (1H, dd, J = 9.79, 2.38 Hz), 4.13 (1H, d, J = 10.08 Hz), 3.52 (1H, qd, J = 10.46, 7.00 Hz), 3.07 (1H, dd, J = 10.30, 2.91 Hz), 1.86 (3H, s), 1.59 (3H, d, J = 6.91 Hz).; ^{13}C NMR: δ ppm 167.4, 150.2, 147.5, 143.4, 128.8, 127.8, 127.2, 126.5, 123.8, 72.3, 66.8, 40.4, 19.3, 12.0.

(2*S*,3*S*,1′*R*)-2-[(4-Bromo-phenyl)-hydroxy-methyl]-3-phenyl-butyric Acid Methyl Ester (11c). The compound was obtained using general procedure A from thioester **8** (0.50 mmol, 90 mg) and 4-bromobenzaldehyde (1.00 mmol, 185 mg). After purification, title compound **11c** was isolated as a white solid (123 mg, 68%, >20:1 dr, 95% ee based on analysis of 1,4-addition product **10** prior to aldol coupling): mp 118.5−120.0 °C; $[\alpha]_D$ −14.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR: δ ppm 7.44−7.21 (6 H, m), 7.02 (2 H, d, J = 8.58 Hz), 4.38 (1 H, dd, J = 9.64, 3.14 Hz), 3.77 (1 H, d, J = 9.62 Hz), 3.56 (3 H, s), 3.37 (1 H, qd, J = 10.86, 6.93 Hz), 2.88 (1 H, dd, J = 10.83, 3.15 Hz), 1.28 (3 H, d, J = 7.00 Hz), 1.13 (3 H, d, J = 6.86 Hz). ^{13}C NMR: δ ppm 175.2, 143.4, 141.7, 131.3, 128.8, 127.4, 127.0, 126.8, 121.1, 71.33, 59.2, 51.7, 39.5, 20.2. HRMS: calcd for $C_{18}H_{19}O_3BrNa$ ($M + Na^+$), 385.0415; found, 385.0380.

(2*S*,3*S*,1′*R*)-2-[(4-Methoxy-phenyl)-hydroxy-methyl]-3-phenyl-butyric Acid Methyl Ester (11d). The compound was obtained using general procedure A from thioester **8** (0.50 mmol, 90 mg) and 4-methoxybenzaldehyde (1.00 mmol, 136 mg). After purification, title compound **11d** was isolated as a white, semisolid (85 mg, 54%, >20:1 dr, 95% ee based on analysis of 1,4-addition product **10** prior to aldol coupling): $[\alpha]_D$ −2.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR: δ ppm 7.40−7.24 (5H, m), 7.10 (2H, d, J = 8.74 Hz), 6.83 (2H, d, J = 8.79 Hz), 4.46 (1H, dd, J = 9.13, 3.78 Hz), 3.80 (3H, s), 3.66−3.50 (4H, m), 3.36 (1H, qd, J = 10.37, 7.06 Hz), 2.94 (1H, dd, J = 10.38, 3.81 Hz), 1.30 (3H, d, J = 7.05 Hz). ^{13}C NMR: δ 175.3, 158.8, 143.8, 134.7, 128.7, 127.5, 126.8, 126.3, 113.7, 71.6, 59.5, 55.2, 51.5, 39.4, 19.8. HRMS: calcd for $C_{19}H_{22}O_4Na$ (M + Na^+), 337.1410; found, 337.1398.

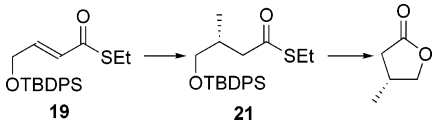
(2*S*,3*S*,1′*S*)-3-Hydroxy-2-(1-phenyl-ethyl)-octanoic Acid Methyl Ester (11e). The compound was obtained using general procedure A from thioester **8** (0.50 mmol, 90 mg) and hexanal (1.00 mmol, 100 mg). After purification, title compound **11e** was isolated as a clear oil (103 mg, 74%, >20:1 dr, 95% ee based on analysis of 1,4-addition product **10** prior to aldol coupling): $[\alpha]_D$ +1.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ ppm 7.58−7.11 (5H, m), 3.81 (3H, s), 3.37 (1H, qd, J = 11.06, 7.00 Hz), 3.20 (1H, s), 2.68 (1H, s), 2.61 (1H, dd, J = 11.11, 2.58 Hz), 1.51−1.04 (11H, m), 0.85 (3H, t, J = 7.20 Hz). ^{13}C NMR: δ 175.8, 144.0, 128.7, 127.5, 126.7, 70.1, 57.2, 51.7, 39.1, 36.6, 31.6, 25.7, 22.5, 20.5, 14.0. HRMS: calcd for $C_{17}H_{26}O_3Na$ (M + Na^+), 301.1774; found, 301.1760.

(2*S*,3*S*,1′*R*)-2-(Cyclohexyl-hydroxy-methyl)-3-phenyl-butyric Acid Methyl Ester (11f). The compound was obtained using **general procedure A** from thioester **8** (0.50 mmol, 90 mg) and cyclohexane carboxaldehyde (1.00 mmol, 112 mg). After purification, title compound **11f** was isolated as a white semisolid (110 mg, 76%, >20:1 dr, 95% ee based on analysis of 1,4-addition product **10** prior to aldol coupling): $[\alpha]_D$ +3.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ ppm 7.41−7.12 (5 H, m), 3.78 (3 H, s), 3.35 (1 H, qd, J = 13.98, 7.01 Hz), 2.99−2.59 (3 H, m), 1.92 (1 H, d, J = 12.78 Hz), 1.79−1.40 (2 H, m), 1.37−0.88 (9 H, m), 0.86−0.55 (2 H, m). ^{13}C NMR: δ ppm 176.1, 144.0, 128.6, 127.4, 126.6, 74.6, 53.9, 51.7, 43.0, 39.3, 29.4, 29.0, 26.2, 25.9, 25.7, 20.7. HRMS calcd for $C_{18}H_{26}O_3Na$ (M + Na^+), 313.1774; found, 313.1786.

(2*S*,3*R*,1′*S*)-3-Hydroxy-4,4-dimethyl-2-(1-phenyl-ethyl)-pentanoic Acid Methyl Ester (11 g). The compound was obtained using general procedure A from thioester **8** (0.50 mmol, 90 mg) and pivalinaldehyde (1.00 mmol, 86 mg). After purification, title compound **11g** was isolated as a clear oil (95 mg, 72%, >20:1 dr, 95% ee based on analysis of 1,4-addition product **10** prior to aldol coupling): $[\alpha]_D$ +9.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ ppm 7.41−7.10 (5 H, m), 3.76 (3 H, s), 3.64 (1 H, d, J = 10.04 Hz), 3.29 (1 H, qd, J = 11.27, 7.00 Hz), 2.82 (1 H, ddd, J = 12.57, 10.60, 1.44 Hz), 1.20 (3 H, d, J = 7.01 Hz), 0.74 (9 H, s). ^{13}C NMR: δ ppm 177.0, 144.1, 128.6, 127.4, 126.7, 78.0, 51.7, 50.8, 40.8, 35.5, 25.6, 20.6. HRMS: calcd for $C_{16}H_{24}O_3Na$ (M + Na^+), 287.1617; found, 287.1610.

(3*S*)-3-(4-Chloro-phenyl)-thiobutyric Acid *S*-Methyl Ester (20). Compound **20** was used to determine enantiomeric excess of tandem 1,4-addition-aldol reactions using thioester **18** as substrate (product **11h**). The compound was prepared using general procedure A and isolated from the reaction mixture prior to aldehyde addition (aldol coupling). Title compound **20** was obtained as a clear oil: $[\alpha]_D$ +59.3 (*c* 0.3, $CHCl_3$). ^{1}H NMR: δ 7.28−7.22 (2H, m), 7.17−7.10 (2H, m), 3.32 (1H, sext, J = 7.1 Hz), 2.88−2.70 (2H, m), 2.25 (3H, s), 1.27 (3H, d, J = 7.0 Hz). ^{13}C NMR: δ 198.1, 143.7, 132.0, 128.5, 128.0, 51.7, 36.3, 21.4, 11.5. HRMS: calcd for $C_{11}H_{13}ClOS$, 228.03756; found, 228.03834. HPLC analysis indicated an enantiomeric excess of >99% [Chiralcel OD-H column; flow, 0.5 mL/min; heptane/*i*-PrOH, 99.5/0.5; 210 nm; minor enantiomer (−)-**20**, t_R = 10.9; major enantiomer (+)-**20**, t_R = 12.3 min].

(2*S*,3*S*,1′*R*)-3-(4-Chloro-phenyl)-2-(hydroxy-phenyl-methyl)-butyric Acid Methyl Ester (11h). The compound was obtained using general procedure A from thioester **18** (0.50 mmol, 106 mg) and benzaldehyde (1.00 mmol, 100 mg). After purification, title compound **11h** was isolated as a white solid (78 mg, 49%, >20:1 dr, >99% ee based on analysis of 1,4-addition product **20** prior to aldol coupling): mp 78.5−80.4 °C; $[\alpha]_D$ −9.9 (*c* 1.4, $CHCl_3$). ^{1}H NMR δ 7.39−7.22 (7 H, m), 7.17 (2 H, d, J = 7.60 Hz), 4.47 (1 H, dd, J = 9.27, 3.53 Hz), 3.66 (1 H, d, J = 9.39 Hz), 3.56 (3 H, s), 3.37 (1 H, qd, J = 10.67, 7.02 Hz), 2.91 (1 H, dd, J = 10.48, 3.73 Hz), 1.29 (3 H, d, J = 7.04 Hz). ^{13}C NMR: δ 175.0, 142.3, 132.5, 129.0, 128.8, 128.4, 128.3, 127.4, 125.0, 72.0, 59.5, 51.7, 38.8, 19.8. HRMS: calcd for $C_{18}H_{19}ClO_3Na$ (M + Na^+), 341.0914; found, 341.0918.



(3*S*)-4-(*tert*-Butyl-diphenyl-silanyloxy)-3-methyl-thiobutyric Acid *S*-Methyl Ester (21). Used to determine enantiomeric excess of tandem 1,4-addition-aldol reactions using thioester **19** as substrate (product **11j**). Prepared using general procedure A and isolated from a sample of the reaction mixture prior to aldehyde addition (aldol coupling). Title compound **21** obtained as a clear oil: $[\alpha]_D$ +8.0 (*c* 1.2, $CHCl_3$). ^{1}H NMR: δ 7.66 (4H, dd, J = 6.76, 1.37 Hz), 7.41 (6H, m), 3.55 (1H, dd, J = 9.95, 5.27 Hz), 3.46 (1H, dd, J = 9.94, 6.27 Hz), 2.88 (2H, q, J = 7.43 Hz), 2.83 (1H, dd, J = 14.46, 5.27 Hz), 2.38 (1H, dd, J = 14.47, 8.43 Hz), 2.28 (1H, m), 1.25 (3H, t, J = 7.43 Hz), 1.15 (9H, s), 0.98 (3H, d, J = 6.63 Hz). ^{13}C NMR: δ 199.1, 135.6, 133.6, 129.6, 127.5, 67.90, 47.8, 33.8, 26.8, 23.3, 19.3, 16.4, 14.8. For determination of enantiomeric excess, compound **21** was treated with TBAF to yield a pure sample of (*R*)-4-methyl-dihydrofuran-2-one: $[\alpha]_D$ = +21.6 (*c* 0.5, MeOH), lit. [for (*S*)-4-methyl-dihydrofuran-2-one] = −24.7 (*c* 1.7, MeOH).[17] Determination of enantiomeric excess was achieved by GC analysis [Chiraldex AT-A (30.0 m × 0.25 mm), 1.0 mL min^{-1}, initial temp is 50 °C then 5 °C min^{-1} to final temp of 170 °C, 19.7 min (minor), 19.9 min (major) shows 98% ee].

4-(2,2-Dimethyl-1,1-diphenyl-propoxy)-2-(hydroxy-phenyl-methyl)-3-methyl-thiobutyric Acid *S*-Methyl Ester (11j). The compound was obtained using general procedure A from thioester **19** (0.72 mmol, 330 mg) and benzaldehyde (1.40 mmol, 148 mg). Flash column chromatography gave the title compound **11j** (184 mg, 50%, ~1:1 dr, 98% ee based on analysis of 1,4-addition product **21** prior to aldol coupling). Repeated chromatography (20:1 Et_2O/pentane) allowed separation of diastereomers. **First diastereomer**: $[\alpha]_D$ −63.3 (*c* 4.2, $CHCl_3$). ^{1}H NMR: δ ppm 7.71−7.64 (4H, m), 7.50−7.24 (11H, m), 5.04 (1H, dd, J = 4.2, 8.8 Hz), 3.61 (1H, dd J = 4.7, 10.3 Hz), 3.58−3.52 (2H, m), 3.09 (1H, dd, J = 4.2, 8.4 Hz), 2.74−2.60 (2H, m), 2.38−2.28 (1H, m), 1.20 (3H, m), 1.08 (9H, s), 1.00 (3H, t, J = 7.4 Hz). ^{13}C NMR: δ 203.8, 142.3, 135.6, 135.6, 133.5, 133.4, 129.5, 128.1, 127.5, 127.5, 127.2, 125.6, 72.6, 72.5, 66.3, 66.3, 66.3, 61.9, 61.9, 36.7, 26.9, 26.9, 23.2, 19.2, 15.2, 14.3, 14.2. HRMS: $C_{26}H_{29}O_3SSi$ (M^+ − *t*-Bu): calcd, 449.16066; found, 449.15948. **Second diastereomer**: $[\alpha]_D$ +10.6 (*c* 3.9, $CHCl_3$). ^{1}H NMR: δ ppm 7.66 (2H, m), 7.59 (2H, m), 7.50−7.23 (11H, m), 5.07 (1H, t, J = 6.6 Hz), 3.70 (1H, dd, J = 4.6, 10.4 Hz), 3.64 (1H, dd, J = 6.2, 10.4 Hz), 3.36 (1H, t, J = 6.4 Hz), 3.15 (1H, d, J = 7.2 Hz), 2.79 (2H, dq, J = 1.9, 7.4 Hz), 2.04 (1H, dq, J = 4.8, 6.6 Hz), 1.13 (3H, t, J = 7.4 Hz), 1.09 (9H, s), 0.94 (3H, d, J = 7.0 Hz). ^{13}C NMR: δ 203.0, 142.2, 135.9, 135.7, 133.7, 133.6, 129.9, 128.6, 127.9, 126.3, 73.7, 73.7, 66.3, 61.5, 35.8, 27.1, 27.1, 23.7, 19.6, 14.8, 14.7, 14.7. HRMS: $C_{26}H_{29}O_3SSi$ (M^+ − *t*-Bu): calcd, 449.16066; found, 449.15927.

(2*S*,3*S*,4*S*)-4-Methyl-5-oxo-2-pentyl-tetrahydro-furan-3-carboxylic Acid [(−)-Phaseolinic Acid (22)]. Succinic acid derivative **24** (75

(17) (a) Leuenberg, H. G. W.; Boguth, W.; Barner, R.; Schmid, M.; Zell, R. *Helv. Chem. Acta* **1979**, *62*, 455−463. (b) Mukayama, T.; Fujimoto, K.; Hirose, T.; Takeda, T. *Chem. Lett.* **1980**, 635. (c) Mori, K. *Tetrahedron* **1983**, *39*, 3107−3109.

mg, 0.21 mmol, 1.00 equiv) was dissolved in aqueous HBr (48%, 15 mL) and heated to reflux with stirring for 3 h. The mixture was cooled and water (10 mL) was added. The mixture was extracted with EtOAc (4 × 15 mL), and the combined organic phases were washed (brine) and dried ($MgSO_4$), and the solvent evaporated to give a pale brown solid. Crystallization (hexane/EtOAc) gave title compound **22** (38 mg, 91%) as a white solid: mp 142.0−144.0 °C (lit. 138−140 °C,[15f] 137−138 °C[15b]); $[\alpha]_D$ −145.4 (*c* 0.5, $CHCl_3$) [lit. −142 (0.22, $CHCl_3$),[15f] −147 (0.37, $CHCl_3$)[15b]]. ^{1}H NMR: δ ppm 4.87−4.62 (1 H, m), 3.25 (1 H, t, J = 8.94 Hz), 3.07 (1 H, qd, J = 14.24 Hz), 1.71−1.16 (11 H, m), 0.91 (1 H, t, J = 6.53 Hz), ^{13}C NMR: δ 177.4, 174.8, 77.3, 51.6, 36.4, 31.3, 31.1, 25.3, 22.4, 14.4, 13.9.

(2*S*,3*S*,1′*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-(1-phenyl-ethyl)-octanoic Acid Methyl Ester (23). Tandem product **11e** (170 mg, 0.61 mmol, 1.00 equiv) was dissolved in dry THF (10 mL) and stirred under N_2. To this solution was added 2,6-lutidine (90 μL, 0.70 mmol, 1.20 equiv) and TBDMS−OTf (175 μL, 0.70 mmol, 1.20 equiv). The mixture was stirred at room temperature for 3 h before addition of aqueous NH_4Cl (saturated) and Et_2O (10 mL). The organic phase was separated and washed with brine, dried ($MgSO_4$), and evaporated to give a clear oil. Flash column chromatography (25:1 hexane/EtOAc) gave title compound **23** (225 mg, 94%) as a clear oil. ^{1}H NMR: δ ppm 7.38−7.13 (5 H, m), 3.86−3.77 (1 H, m), 3.68 (3 H, s), 3.22 (1 H, qd, J = 14.01, 6.95 Hz), 2.90 (1 H, dd, J = 8.95, 5.61 Hz), 1.69−1.03 (14 H, m), 0.95 (9 H, s), 0.06 (3 H, s), 0.05 (3 H, s). ^{13}C NMR: δ ppm 173.2, 144.9, 128.4, 127.4, 126.4, 71.7, 56.4, 51.0, 38.9, 35.0, 31.9, 25.8, 23.4, 22.6, 19.4, 18.1, 14.0, −3.9. HRMS: calcd for $C_{23}H_{41}O_3Si$, 393.2819; found, 393.2828.

(2*S*,3*S*,1′*S*)-2-[1-(*tert*-Butyl-dimethyl-silanyloxy)-hexyl]-3-methyl-succinic Acid 1-Methyl Ester (24). Methyl ester **23** (130 mg, 0.33 mmol, 1.00 equiv) was dissolved in MeCN (1.50 mL), EtOAc (1.50 mL), and water (15 mL) and stirred at room temperature for 5 min. To the flask was added $NaIO_4$ (3.90 g, 18.0 mmol, 55.0 equiv) followed by $RuCl_3 \cdot xH_2O$ (8 mg, 0.04 mmol, 0.09 equiv). The mixture was stirred and became brown over ∼5 min, then a white suspension formed over ∼16 h. After this time, water (20 mL) was added, and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic phases were washed (brine) and dried ($MgSO_4$), and the solvent evaporated to give a brown/black oil which was purified by column chromatography (5:1 hexane/EtOAc) directly to give title compound **24** (105 mg, 88%) as a clear oil. ^{1}H NMR δ ppm 4.02−3.89 (1 H, m), 3.71 (1 H, s), 3.02−2.89 (2 H, m), 1.72−1.16 (11 H, m), 1.01−0.79 (12 H, m), 0.07 (6 H, s). ^{13}C NMR: δ ppm 180.9, 171.9, 71.9, 52.5, 51.4, 38.5, 35.0, 31.9, 25.8, 24.2, 22.6, 18.0, 15.5, 14.0, −4.2. HRMS calcd for $C_{18}H_{36}O_5SiNa$ ($M + Na^+$), 383.2224; found, 383.2228.

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Supporting Information Available: NMR spectra (^{1}H and ^{13}C NMR) and HPLC chromatograms are available for all novel compounds along with crystallographic data for structures **11a** and **12b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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