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Acyclic 1,4-Stereocontrol via the Allylic Diazene Rearrangement: Development, Applications, and the Essential Role of Kinetic E-Stereoselectivity in Tosylhydrazone Formation

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ABSTRACT

We report full details of a method for 1,3-reductive transposition of α-alkoxy-α,β-unsaturated hydrazones to provide *E*-alkenes with high 1,4-stereocontrol between the two respective allylic stereocenters. The process couples a chelation controlled reduction of the hydrazone with an in situ allylic strain controlled retro-ene reaction of an allyl diazene, i.e. an allylic diazene rearrangement. Such stereotriads are frequently observed motifs in natural products. We observed a fortuitous kinetic preference for the *E*-hydrazone geometry during the hydrazonation reaction, as only the *E*-isomers could undergo chelation-controlled reduction.

INTRODUCTION

Several years ago, we considered undertaking the total synthesis of antascomicin B (**1**), a macrolide isolated from a *Streptomyces* strain that binds with high affinity to FKBP12 (Figure 1).[1,2,3] We noted two pairs of stereochemical relationships in the molecule: First, a 1,2-*anti* relationship between the C26 alkoxy and C27 methyl stereocenters, and a 1,2-*syn* relationship between the C14 alkoxy and C15 methyl stereocenters; second, a 1,4-*anti* relationship between the C14 hydroxy and C11 methyl stereocenters, and a 1,4-*syn* relationship between the C26 alkoxy and C23 methyl stereocenters. We recognized immediately that Ireland-type Claisen rearrangements would be well suited to introduce the 1,2-*syn* and 1,2-*anti* alkoxy and alkyl

stereocenters at C26-C27 and C14-C15.[4] We reasoned that the C14 and C26 alkoxy stereocenters could potentially be employed as the source of stereocontrol for the remote C11 and C23 stereocenters, respectively, via a stereochemical relay to engender the requisite 1,4-*syn* or 1,4-*anti* stereocontrol (vide infra).

In addition to antascomicin B, there are numerous bioactive natural products that possess 2° oxygen and 3° alkyl containing stereocenters in a 1,4-*syn* or 1,4-*anti* relationship.[5,6,7,8,9,10,11,12] There are yet additional natural products with 1,4-*syn* and 1,4–*anti* relationships in which the stereocenters are separated by an intervening *E*-alkene, such as divergolide B and jerangolid D (Figure 1).[13,14,15,16,17,18,19,20,21,22,23,24,25,26] Since hydrogenation of the intervening alkene could provide the dihydro adducts needed for natural products such as antascomicin B, a general method for the preparation of *E*-1,4-*syn* and *E*-1,4-*anti* stereotriads (inset) had the potential to be broadly useful in complex molecule synthesis, and hence became our immediate goal.

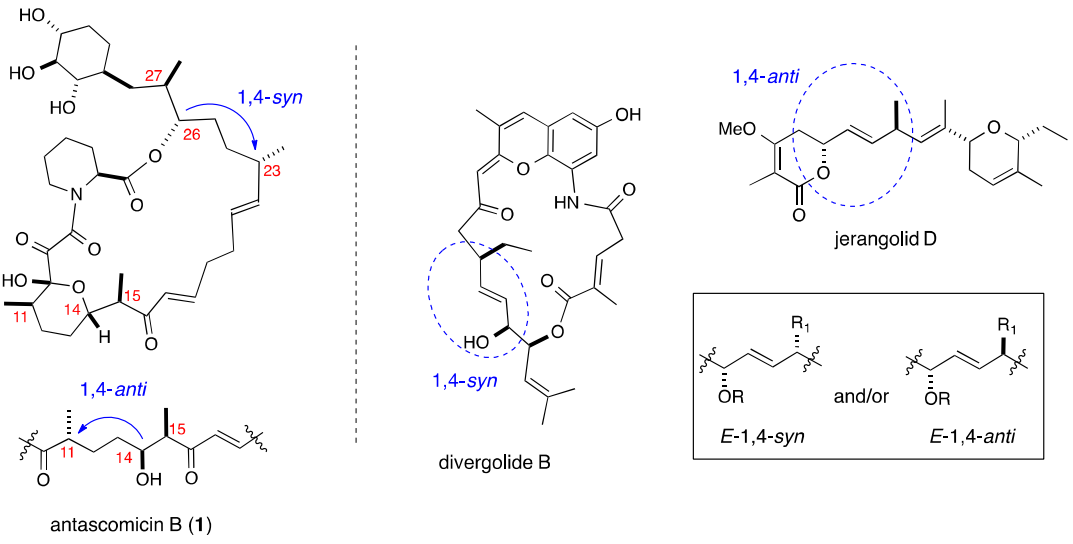
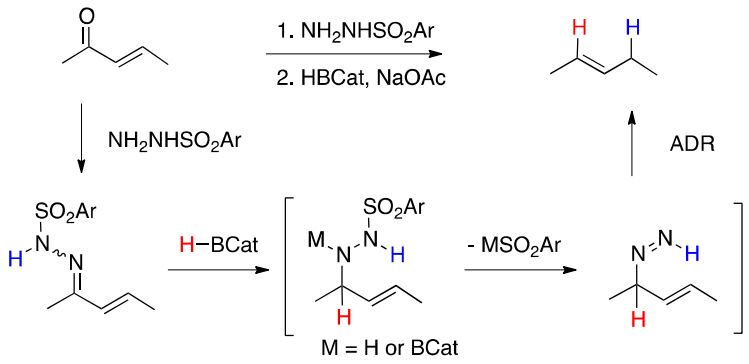


Figure 1: Representative bioactive natural products containing 1,4-*syn* and *anti*-stereorelationships.

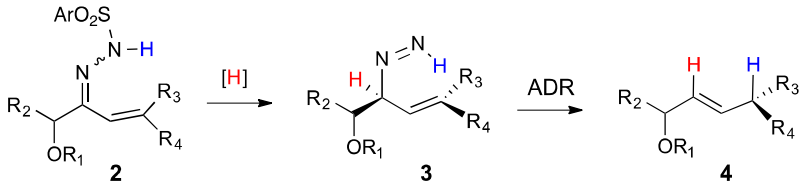
In 1976 Kabalka reported a modification[27] of an earlier procedure by Hutchins[28] of a reductive transposition of an α,β-unsaturated ketone to a 1,2-rearranged propene (Scheme 1). The two-step transformation involves an initial conversion of the enone to the corresponding sulfonyl hydrazone. In the second step, a 1,2-reduction of the hydrazone with catecholborane (HBCat) is followed by *in situ* formation of an allylic diazene. The diazene suffers spontaneous retro-ene reaction with delivery of the diazene hydrogen to the terminus of the alkene.[29] The retro-ene reaction is known as the allylic diazene rearrangement (ADR).[30]



Scheme 1

We[31] and many others[32] have employed this protocol in diastereoselective reductive transpositions of cyclic enones in complex molecule synthesis. However, prior to our work,[33] there were no reports of its use in any acyclic systems to generate sp^3 stereocenters.[34]

We reasoned that the sulfonyl hydrazone of an α-chiral α-alkoxy enone **2** could be reduced diastereoselectively via either a Cram chelation[35,36,37] or a Felkin-Anh type pathway[38] to provide intermediate allyl diazene **3** (Scheme 2). Allylic strain directed rearrangement[39,40,41] would deliver the diazene hydrogen to the prochiral allylic carbon diastereoselectively.



Scheme 2

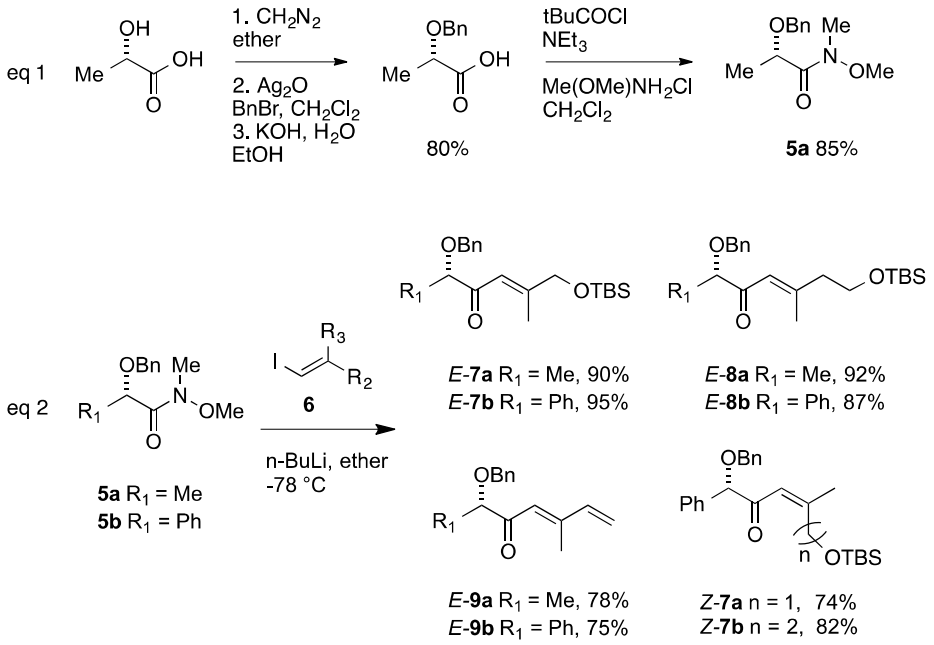
Three issues were of concern at the project's outset: (i) whether the hydrazones of the comparatively hindered enones could be readily prepared; (ii) whether the *E/Z* configuration of the hydrazone would be relevant, and if so, (iii) whether the *E/Z* configuration of the hydrazone could be controlled.

RESULTS AND DISCUSSION

Methodological Studies – Enone Synthesis. We prepared a variety of α-chiral α-alkoxy enones from (*S*)-(+)-lactic and either racemic or (*S*)-(+)-mandelic acid to test our hypothesis. Weinreb amide **5a** was prepared by methylation of (*S*)-(+)-lactic acid with diazomethane, followed by etherification of the alcohol and ester hydrolysis to provide *O*-benzyl lactic acid in high yield (eq 1, Scheme 3). The amide **5a** was prepared via the mixed anhydride. While **5a** was formed without detectable racemization, (*S*)-(+)-mandelic acid underwent partial racemization, likely at the etherification step, to give a ca. 3:1 er of amide **5b**.[42]

Addition of various vinyl Li nucleophiles derived from readily accessible vinyl iodides **6** to the Weinreb amides **5a** and **5b** provided the requisite E-enones *E*-**7a,b**, **8a,b**, and **9a,b, and** and Z-enones *Z*-**7a**,**b** in good to excellent yields (eq 2, Scheme 3). The siloxymethyl,

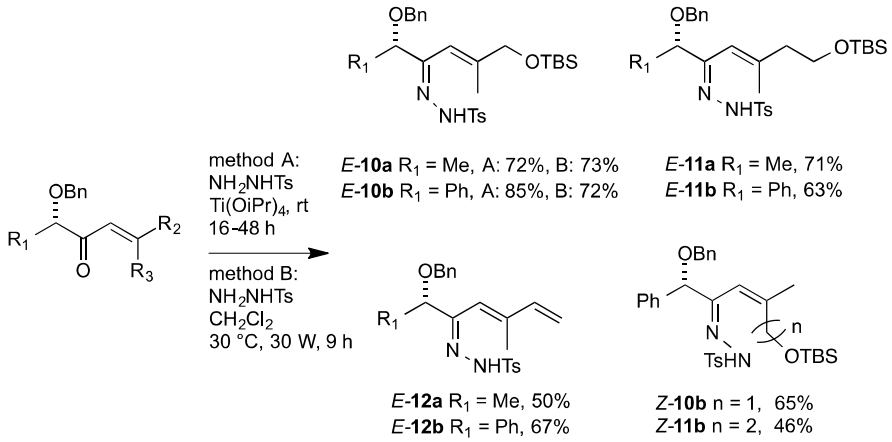
siloxyethyl, and terminal vinyl substituents of the enones were chosen because they are synthetically flexible groups, and could be elaborated in numerous ways.



Scheme 3

Hydrazonation Reactions – Kinetic Selectivity for *E*-Hydrazone. With the requisite enones in hand, the next step was to form the tosyl hydrazones. Tosyl hydrazones of enones have been typically prepared by heating an alcoholic solution of the enone with tosyl hydrazide with or without an acid catalyst. However, we found these and a variety of related conditions to be unsatisfactory, giving incomplete conversion and/or undesired side products. Treatment of enone *E*-**7a**, for example, with tosyl hydrazide and ethanol gave the desired hydrazone, but also desilylated and deconjugated[43] hydrazones.

After some experimentation, we discovered that simply mixing the enone with tosyl hydrazide in neat $Ti(OiPr)_4$ at ambient temperature yielded the hydrazones in generally good yields (method A, Scheme 4). Under these conditions, the *E*-hydrazone isomer predominated and could be isolated in pure form by either crystallization or chromatography. We later found that hydrazones ***E*-10a** and ***E*-10b** could be prepared by treatment with $TsNHNH_2$ in CH_2Cl_2 under microwave irradiation to yield solely the *E*-hydrazones in similar yield and shorter reaction time (method B).



Scheme 4

The *E/Z* configuration of the hydrazones was determined by ^1H NMR analysis (Figure 2). Hydrogen bonding of the sulfonamide proton in the *Z*-hydrazone results in a ca. 2 ppm downfield shift relative to the *E*-isomer.[44]

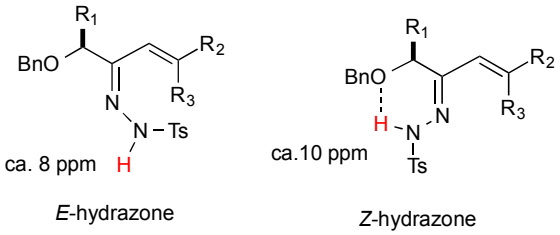
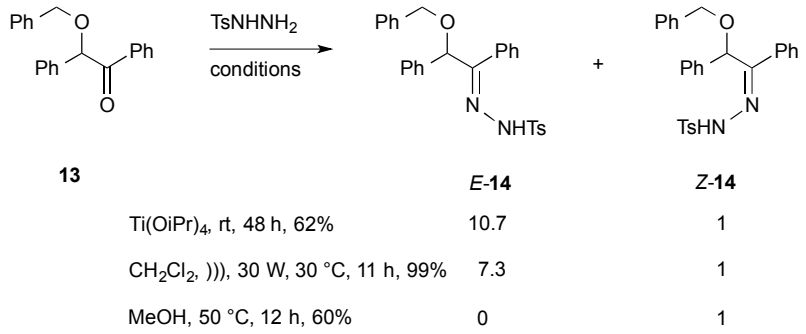


Figure 2: Approximate ^{1}H-NMR shifts of hydrazone N-H protons in *E*- and *Z*-hydrazones.

The *E*-selectivity proved to be fortuitous (vide infra), and we subsequently studied the issue both experimentally and computationally. We employed *O*-benzylbenzoin (**13**) as a model system for α-alkoxy ketones (Scheme 5). Treatment of **13** with $TsNHNH_2$ in neat $Ti(OiPr)_4$ for 48 h provided a 10.7:1 *E:Z* mixture of hydrazones **14** in 62% yield. We found that irradiating a methylene chloride solution of **13** and $TsNHNH_2$ in a microwave for 11 h at 30 °C and 30 watts gave a quantitative yield of a 7.3:1 *E:Z* mixture of hydrazones **14**. Surprisingly, heating the reaction mixture in methanol completely reversed the selectivity to provide solely the *Z*-hydrazone.



Scheme 5

These results imply that both the thermodynamic and kinetic hydrazone isomers can selectively be formed by appropriate choice of conditions, but it was not clear which isomer is the kinetic and which is the thermodynamic. We therefore carried out DFT calculations (B3LYP/6-31g*) of simplified *E*- and *Z*-hydrazones (Figure 3). We believe that the tolyl group on the sulfone moiety of hydrazones **14** is remote enough that truncating it to a methyl group for computational simplicity would have negligible effect on the calculated energy difference between the *E*- and *Z*-isomers.

The calculations predict a modest preference for the *Z*-hydrazone driven by internal hydrogen bonding between the ether oxygen and the sulfonamide nitrogen. Hence the *E*-hydrazone would be the kinetic isomer, at least in the case of *O*-alkyl benzoin sulfonyl hydrazones, and the *Z*-hydrazone the thermodynamic.

The *Z/E* energy difference is significantly larger for the hydrazones derived from terminally disubstituted enones, with the *E*-isomer calculated to be 5.3 kcal/mol higher in energy than the hydrogen-bonded *Z*-isomer. There is a loss of conjugation in the *E*-isomer between the C=N and C=C double bonds as reflected in the large dihedral angle (64.8°) between them as a consequence of the steric interaction between the alkene and the sulfonamide moiety. The *Z*-isomer lacks this interaction, and has a much smaller dihedral angle (21.6°) and better overlap across the heterodiene system. This makes the observed *Z:E* ratio of hydrazones **10**-**12** all the more remarkable (1-9:1 *E/Z* in neat $Ti(OiPr)_4$, and >20:1 in CH_2Cl_2 under microwave irradiation).

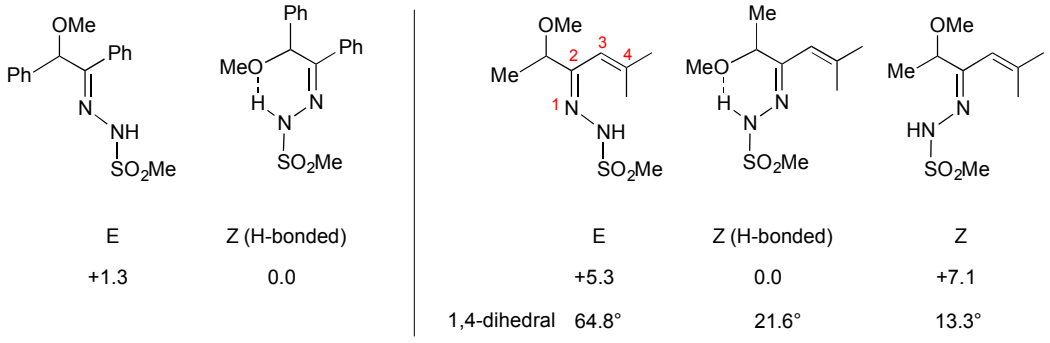
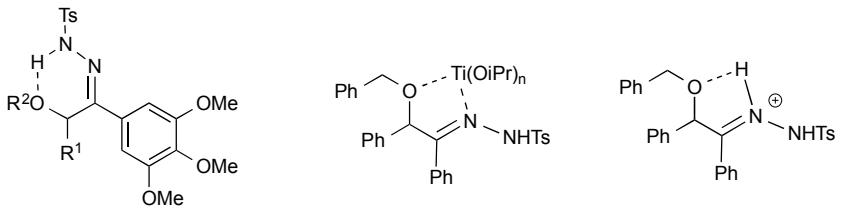


Figure 3: DFT calculations (B3LYP/6-31g*) of simplified *E*- and *Z*-hydrazones

These computational results were supported experimentally. Treatment of a $CDCl_3$ solution of *E*-**14** with a stoichiometric amount of CF_3CO_2H resulted in ca. 1:1 mixture of *E*- and *Z*-isomers after 4 h at ambient temperature.

There are a just a handful of reports of the preparation of acyclic α-alkoxy sulfonyl[45,46,47,48,49,50] or acyl[51,52] hydrazones from ketones, and only a few that report the hydrazone *E/Z*-configurations.[53,54,55,56] Alami et al reported a 1.5-5.7:1 *Z:E* ratio of hydrazones **15** depending upon the identity of R^1 and R^2 (Figure 4). The hydrazones were prepared by stirring the ketones with $TsNHNH_2$ in methanol at ambient temperature. This is consistent with our observation that the reaction in methanol was selective for the *Z*-hydrazone (cf. Scheme 5). The authors proposed internal H-bonding to be the driving force for the *Z*-selectivity, which is also consistent with our computational results.

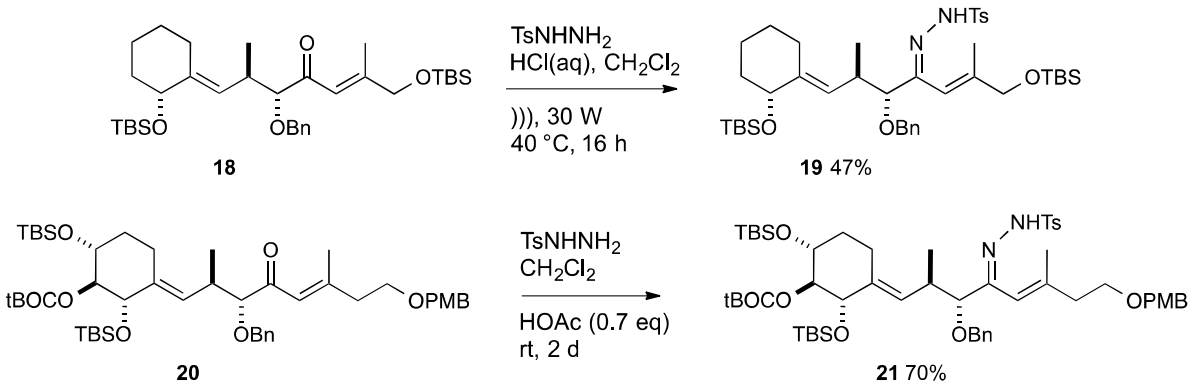
We speculate that the *E*-hydrazones were formed by complexation with $Ti(OiPr)_4$ (**16**, Figure 4). The reason for the high *E*-selectivity under microwave conditions in CH_2Cl_2 is unclear (cf. Scheme 4, 11). Chlorinated solvents are well known to produce trace amounts of HCl, so perhaps a chelated proton as in **17**, analogous to the model proposed for chelation control in the reduction step (vide infra, Scheme 7), could favor the *E*-isomer.



15 **16** **17**

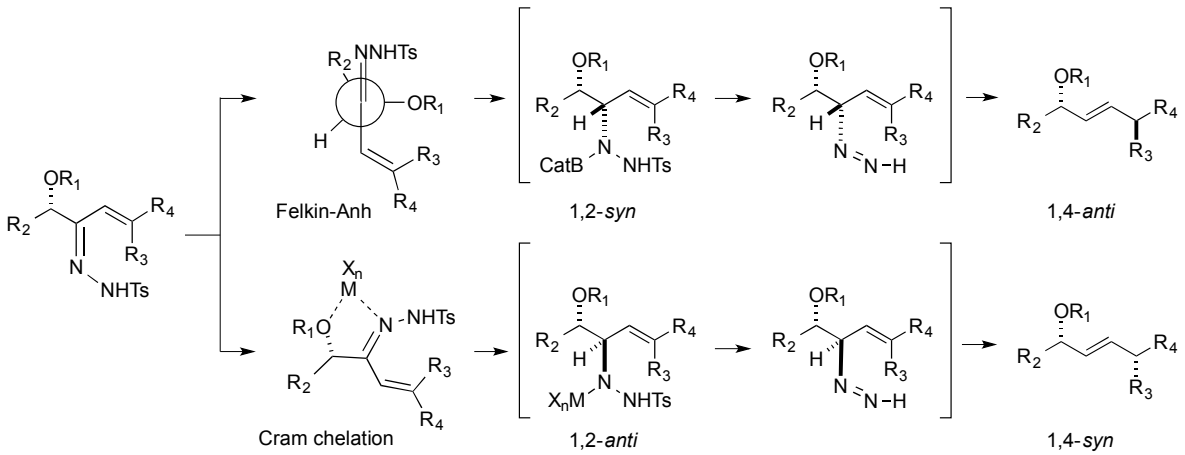
Figure 4: Possible complexation modes of *E*-Hydrazones bearing α-alkoxy substituents.

We found the *E*-selectivity carried over to more complex examples as well, although in these cases exogenous acid was added. Treatment of ketone **18** under the microwave conditions provided *E*-hydrazone **19** as a single isomer, albeit in moderate yield (Scheme 6).[57] Reaction of ketone **20** with $TsNHNH_2$ in CH_2Cl_2 at ambient temperature without microwave irradiation, but with 0.7 eq of HOAc added, provided *E*-hydrazone **21** after 2 days in good yield.[58]



Scheme 6

Chelation Controlled *E*-hydrazone Reduction. In our initial planning, we hoped to identify conditions whereby either the 1,4-*syn* or 1,4-*anti* product could be prepared from the same hydrazone. A Felkin-Anh pathway would give 1,2-*syn* selective reduction, which would provide a net 1,4-*anti* product after the ADR; a Cram chelation pathway would give 1,2-*anti* reduction and a net 1,4-*syn* product (Scheme 7). Hence we reasoned that catecholborane, which cannot chelate, would provide the 1,4-*anti* product, and $Zn(BH_4)_2$ which is known to give chelation controlled reduction of α-alkoxy enones,[59,60] should provide the 1,4-*syn* product.

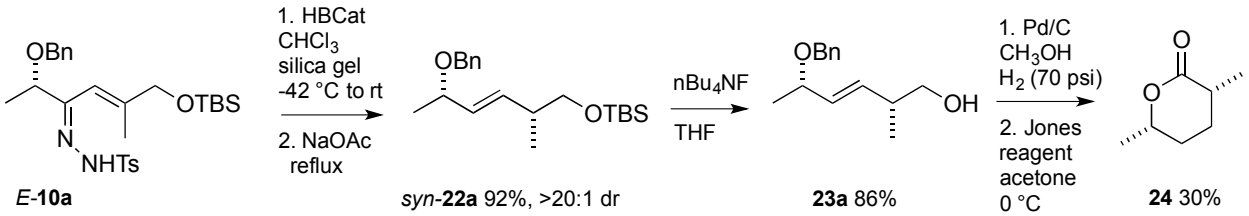


Scheme 7

Most literature procedures employing the Kabalka protocol use only a small excess of catecholborane in the reduction of the tosylhydrazone. However, tosylhydrazone *E*-**10b** reacted sluggishly with 5 eq of borane at -42 °C, requiring 22 h to completely reduce. Isomer *Z*-**10b** reacted even more slowly, providing only low yield of product after 2 days at ambient temperature in the presence of 20 eq of borane.

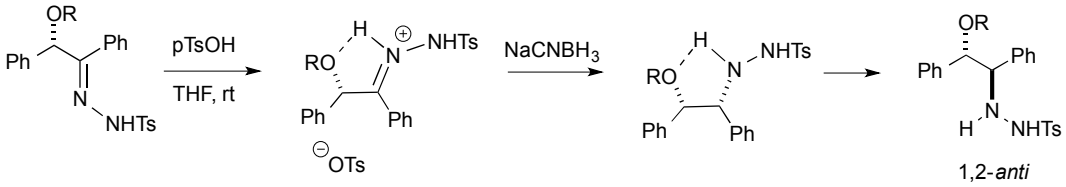
We fortuitously discovered that addition of silica gel (2 weight eq) to the reaction mixture greatly accelerated the reduction step, such that it could be performed using 5 eq of catecholborane at -42 °C within 1 hour. Treatment of *E*-**10a** under these conditions provided alkene *syn*-**22a** in 92% yield with high diastereoselectivity (Scheme 8). The relative configuration was determined by its conversion to the known[61] lactone **24** via cleavage of the TBS ether to give alcohol **23a**, followed by simultaneous hydrogenation of the alkene and hydrogenolysis of the benzyl group. Jones oxidation of the diol provided *cis*-2-methyl-5-hexanolide (**24**). This stereochemical outcome was the opposite of what we expected. The *syn*

configuration required a 1,2-*anti* reduction of the hydrazone, which implied a Cram chelation pathway.



Scheme 8

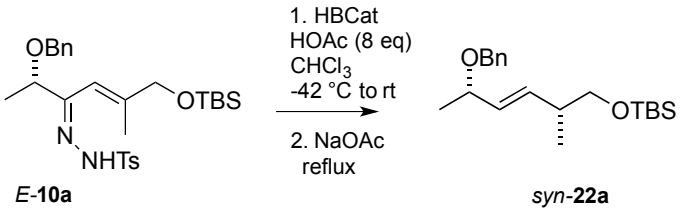
In 1979 Rosini et al had reported the 1,2-*anti* selective reduction of the tosylhydrazones of benzoin (R^1=H) and some *O*-protected derivatives (R^1=Me,Et) at pH 3.5 with $NaCNBH_3$ using pTsOH to maintain the low pH (Scheme 9).[62] Protonation of the hydrazone imine could enable chelation via hydrogen bonding. This model has been proposed by Fujita and Hiyama to rationalize the highly 1,2-*anti* selective reduction of an α-acetoxy-*O*-benzyloxime using $PhMe_2SiH$ in CF_3CO_2H.[63]



Scheme 9

If silica gel was simply a proton source, a soluble, well defined acid would be a more practical reagent, especially on scale. We indeed found that both acetic and trifluoroacetic acids were effective substitutes for silica gel, supporting the hydrogen bond chelation model. Use of acetic acid (6-10 eq) gave higher yields than the stronger trifluoroacetic acid.

In optimizing the reduction of *E*-**10a** for catecholborane, we found that 2.2-2.5 eq gave the best compromise between reaction time and yield on small scale (entries 1-6, Table 1), but as the scale increased, 2.5-3.0 eq were desirable to drive the reaction to completion (entries 8-11).



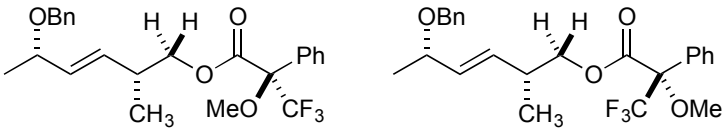
E-**10a** *syn*-**22a**

Table 1. Conversion of *E*-**10a** to *syn*-**22a**.

	HBCat (eq)	Time (h)	Yield (%)	Scale (mg)
1	6	2	97	40
2	4	2	97	"
3	3	4	98	"
4	2.5	2	96	"
5	2.2	2	93	"
6	2	4	75	"
7	2	22	52	"
8	2.5	2	82	100
9	2.5	4	92	"
10	3	4	92	"
11	3	4	85	400

The synthesis of *syn*-**22a** begins with (*S*)-lactic acid (cf. eq 1, Scheme 3). From methyl lactate to hydrazone *E*-**10a**, each intermediate compound was exposed to basic conditions that potentially could racemize the stereocenter. To test for this possibility, Mosher esters (*R*)- and (*S*)-**25** of alcohol **23** were prepared and their ^{1}H-NMR spectra compared (Figure 5). If any racemization had occurred, then the products of Mosher esterification would be a mixture of

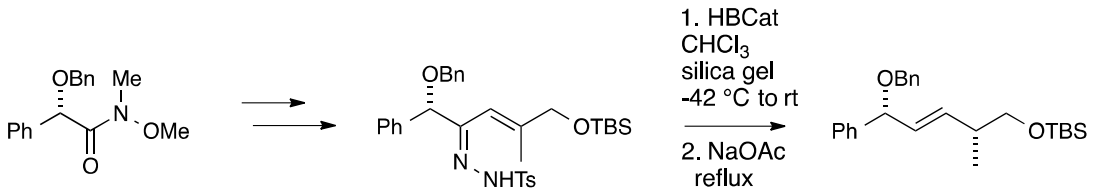
diastereomers consistent with the degree of racemization. In fact, each ester showed a unique set of resonances by ^{1}H- and ^{13}C-NMR analysis.[64]



(*R*)-**25a** (*S*)-**25a**

Figure 5: Mosher esters (*R*)- and (*S*)-**25** of alcohol **23**

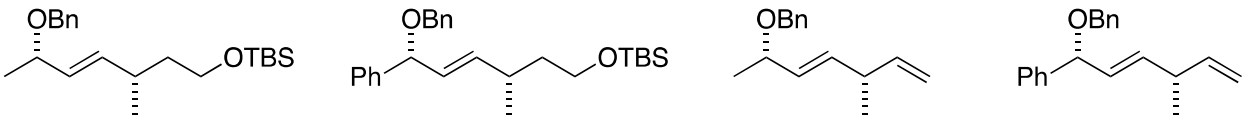
Unlike (*S*)-lactic acid, (*S*)-mandelic acid underwent partial racemization during its conversion from the acid to its Weinreb amide (Scheme 10). Chiral ^{1}H-NMR shift reagent analysis showed a ca. 2.7:1 (*S*):(*R*) enantiomeric ratio of amides. After reductive transposition of *E*-**10b**, ^{1}H-NMR analysis showed **22b** as a single *syn* diastereomer. Mosher ester analysis of the derived alcohol as above gave a 2.6-2.9 dr of Mosher esters, indicating that no significant racemization of the mandelate stereocenter had occurred beyond the stage of amide **5b**. The racemization must have occurred at either the etherification or amidation steps (cf. eq 1, Scheme 3). We are confident that conditions could be found to minimize racemization,[65] but it was not a concern of ours at the time.



5b 2.7:1 er *E*-**10b** *syn*-**22b** 88%

Scheme 10

Using the same protocol, we prepared *syn*-**26a**,**b** and *syn*-**27a**,**b** (Figure 6). In all cases, only the *syn* diastereomer was detectable by ^{1}H-NMR analysis.

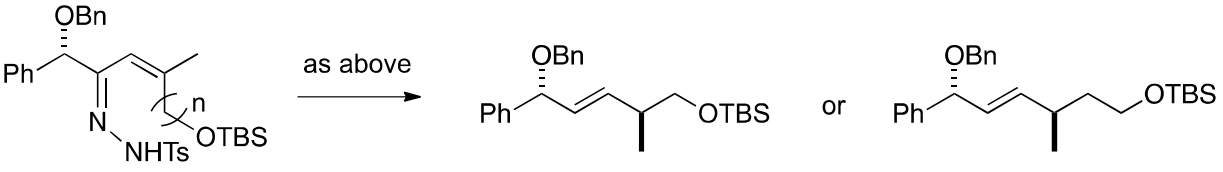


syn-**26a** 85% *syn*-**26b** 83% *syn*-**27a** 81% *syn*-**27b** 95%

Figure 6: *Syn*-alkenes prepared from reductive transpositions of hydrazones.

We compared the conditions reported by Rosini et al in the reduction step to our modified Kabalka conditions (i.e. pTsOH/$NaCNBH_3$/rt vs HBCat/silica gel/-42 °C) for *E*-**11b** and *E*-**12b**, and found the two sets of conditions to give equivalent yields of *syn*-**27b** from *E*-**12b**, but the Rosini conditions to give substantially diminished yields of *syn*-**26b** from *E*-**11b**. The more strongly acidic, higher temperature Rosini conditions may not be as compatible with some types of functionalities.

In order to access the 1,4-*anti* isomers, we treated the *E*-hydrazones possessing *Z*-alkenes *Z*-**10b** and *Z*-**11b** under the silica gel modification of the Kabalka conditions (Scheme 11). The desired 1,4-*anti* products were also obtained a single diastereomers based on ^{1}H-NMR analysis.

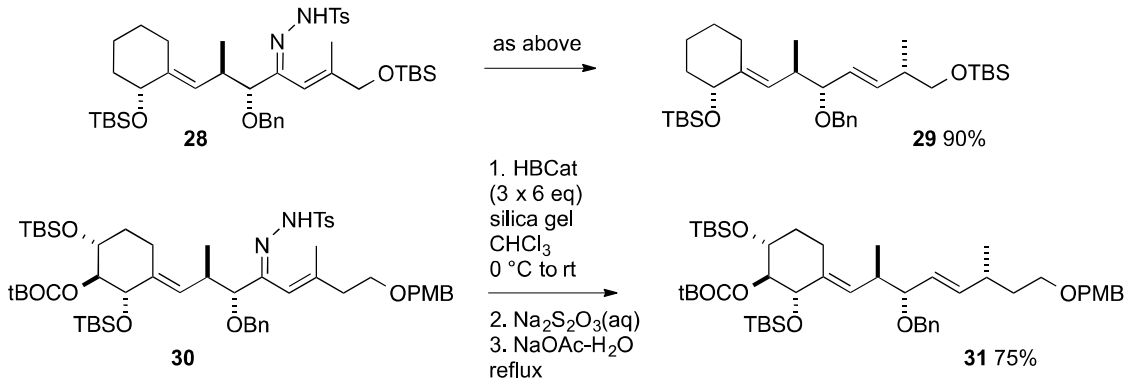


Z-**10b** n = 1
Z-**11b** n = 2

anti-**22b** 85% *anti*-**26b** 80%

Scheme 11

The reductive transposition also performed well in more complex systems (Scheme 12),[57,58] although in the most complex hydrazone **30**, 3 charges of 6 eq of catecholborane were needed to drive the reduction to completion. We speculate that this was due to complexation of the borane by the multiple Lewis basic oxygens. It was necessary to decompose the excess borane prior to heating the mixture with NaOAc to effect the allylic diazene rearrangement, but with that intermediate step included, the overall yield was satisfactory.

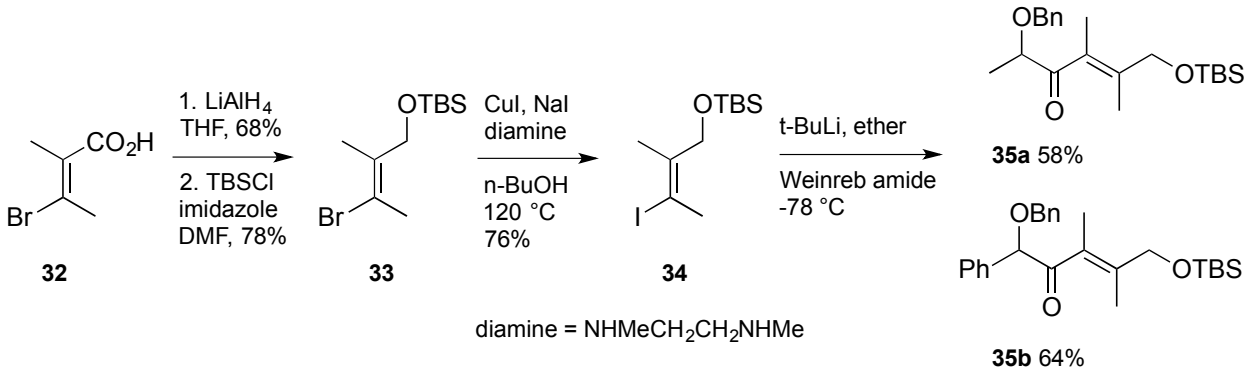


Scheme 12

We sought to extend the method further by employing enones with tetrasubstituted alkenes to provide trisubsubstitued alkenes after rearrangement. To this end, the known *E*-β-bromoangelic acid **32**,[66] prepared in two steps from tiglic acid, was reduced with $LiAlH_4$ and silylated to provide TBS protected allylic alcohol **33** (Scheme 13). Although there is some modest precedent for transmetallation of tetrasubstituted vinyl bromides with alkyl lithium reagents,[67] we were unable to effect any transmetallation of vinyl bromide **33** with either n- or t-butyllithium under a variety of conditions. Using the procedure of Klapars and Buchwald,[68] the bromide was smoothly converted to iodide **34** without alkene isomerization. Transmetallation

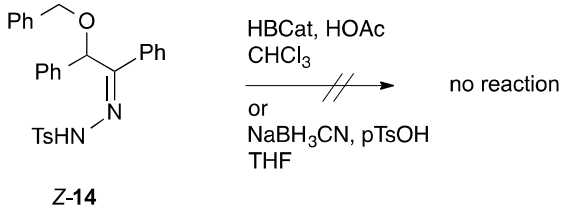
proceeded uneventfully to provide enones **35a** and **35b** upon reaction with the appropriate Weinreb amide.

Unfortunately, despite extensive attempts at hydrazonation of **35a** or **35b** at varying temperatures, with various solvents, catalysts, and hydrazide reagents (tosyl hydrazide, t-butylcarbazate, t-butyl hydrazine), at best equal mixtures of *E*- and *Z*-hydrazones were formed accompanied by inseparable unidentified products. Treatment of the *E/Z*-mixtures of tosyl hydrazones under our standard reductive transposition conditions yielded no identifiable compounds. Presumably the steric congestion about the carbonyl carbon was simply too great to enable efficient hydrazone formation, and we did not pursue the reactions further.



Scheme 13

As mentioned previously, reduction of *E*-hydrazones apparently proceeded by chelation control (cf. Scheme 7). Since *Z*-hydrazones presumably could not effectively chelate, we explored the possibility of their reduction via a Felkin-Ahn pathway. Surprisingly, we found that hydrazone *Z*-**14** (Scheme 14) was impervious to reduction under either the modified Kabalka conditions (HBCat, HOAc, $CHCl_3$) or the Rosini conditions ($NaNCBH_3$, pTsOH, THF).



Z-**14**

Scheme 14

CONCLUSIONS

We have demonstrated that α-alkoxy trisubstituted enones may be converted to *E*-1,4-*syn* or *E*-1,4-*anti* stereotriads via a chelation controlled hydrazone reduction, followed by an in situ allylic diazene rearrangement. The overall 2-step transformation proceeds in generally good yield and excellent diastereoselectivity. The protocol proceeds well with simple as well as complex substrates. The *E*-hydrazone geometry is essential to the success of the hydrazone reduction step; fortunately, we have found conditions under which the *E*-hydrazone can be prepared selectively.

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise noted, all reactions were carried out under a positive pressure of nitrogen. Extractive workup is defined as extraction of the reaction mixture and the indicated aqueous solution three times with ethyl acetate or ether, washing of the combined organic extracts with saturated NaCl solution, drying of the extracts over anhydrous

$MgSO_4$, and concentration in vacuo. Flash column chromatography was performed by employing silica gel (40–63 μm, standard grade, Sorbent Technologies). The same silica gel was used in the indicated reactions. For purification of acid-sensitive *Z*-enones, Florisil (A grade, -200 mesh, Sorbent Technologies) was used.

Materials and Instrumentation. All commercially available compounds were used as received unless otherwise specified. THF, ether, CH_3CN and CH_2Cl_2 were dried over alumina using the solvent purification system. Chloroform (99%) was stabilized by amylenes. Elemental analyses were performed. A chiral capillary column (30m x 0.25mm x 0.12um) was used to analyze enantiopurity. Microwave reactions were performed by using the Discover model CEM Microwave Reactor which has external pressure and temperature sensors. The temperature is sensed by IR whereas the pressure is sensed by the deflection sample lid. A sealed glass reaction vessel was used.

Weinreb amide **5a**.[69] Diazomethane in ether was added to a solution of (*S*)-(+)-lactic acid (1 g, 11 mmol) in ether (10 mL) at 0 °C. After disappearance of starting material, the solution was concentrated in vacuo to give (*S*)-lactic methyl ester (1.1g, 100%). A mixture of Ag_2O (3.1 g, 13.2 mmol), benzyl bromide (2.3 g, 13.2 mmol) and the ester (1.1 g, 10.6 mmol) in CH_2Cl_2 (20 mL) was stirred for 48 h at rt. After filtration, the solution was concentrated to provide the crude benzyl ether. KOH (0.6 g, 10.6 mmol) in water (10 mL) was added dropwise to a solution of ester in ethanol (10 mL) at 0 ^{0}C, and the reaction mixture stirred for 30 min. After extraction with ether (10 mL x 2), the aqueous phase was neutralized with 12 N HCl. The aqueous solution was then extracted with ether (10 mL x 2) and the combined organics dried over $MgSO_4$ and concentrated in vacuo to give *O*-benzyl-(*S*)-lactic acid (1.5 g, 80%).

Trimethylacetyl chloride (1.1 g, 8.9 mmol) was added to a solution of acid (1.5 g, 8.5 mmol) and NEt_3 (0.9 g, 8.9 mmol) at 0 °C. After 30 min, *N*,*O*-dimethyl-hydroxylamine hydrochloride (0.87 g, 8.9 mmol) was added, followed by NEt_3 (1.8 g, 17.8 mmol). The reaction mixture was then allowed to warm to rt and stirred for 16 h. After extractive work-up, the crude material was purified by flash chromatography over silica gel with 5/95 ethyl acetate/hexane to give Weinreb amide **5a** (1.6 g, 85%) as colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4 (d, J=6.6 Hz, 3H), 3.2 (s, 3H), 3.57 (s, 3H), 4.39 (m, 1H), 4.41 (d, J=12 Hz, 1H), 4.67 (d, J=12 Hz, 1H), 7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 32.4, 61.3, 71.2, 71.4, 127.7, 128.9, 128.4, 137.8, 173.9.

Weinreb amide **5b**. Prepared as above for (*S*)-(+)-lactic acid derived Weinreb amide **5a**, (2.05 g, 85%); m.p. 44-46 ^{0}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.18 (s, 3H), 3.35 (s, 3H), 4.63 (s, 2H), 5.31 (s, 1H), 7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.4, 60.9, 70.9, 77.3, 127.8, 128.1, 128.4, 128.6, 136.7, 137.6, 172.0.

Determination of enantiomer ratio of (*S*)-(+)-Weinreb amide **5b**: Europium D-3-trifluoroacetylcamphorate was added in small portions to a sample of Weinreb amide **5b** in chloroform-*d* until baseline separation of the *N*-methyl peak was achieved by ^{1}H NMR (see Supporting Information). Integration of the *N*-methyl peaks revealed a 2.7:1 ratio of enantiomers.

Enone *E*-**7a**. *n*-BuLi (11.5 mL, 2.89 M in hexane, 29.6 mmol) was added to a solution of the known[70] iodide (8.4 g, 26.9 mmol) in ether (30 mL) at -78 °C. After 30 min, the solution was added dropwise to Weinreb amide **5a** (3.0 g, 13.5 mmol) in ether (15 mL). The solution was maintained at -78 ^{0}C until starting material disappeared (approximately 30 min). After extractive

work-up, the crude material was purified by flash chromatography over silica gel with 5/95 ethyl acetate/hexane to give enone *E*-**7a** (4.23 g, 90%) as colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.95 (s, 9H), 1.38 (d, J=6.6 Hz, 3H), 2.11 (s, 3H), 3.98 (q, J=6.9 Hz, 1H), 4.18 (s, 2H), 4.44 (d, J=11.7 Hz, 1H), 4.62 (d, J=11.7 Hz, 1H), 6.84 (s, 1H), 7.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, 16.3, 18.1, 18.3, 25.8, 67.3, 71.7, 81.3, 115.4, 127.7, 127.8, 128.4, 137.9, 159.3; IR (film) cm^{-1} 3031, 1689, 1627, 1116; calcd for $C_{20}H_{32}O_3Si$, C, 68.92; H, 9.25; found, C, 68.65; H, 9.49.

Enone *Z*-**7a**. Prepared as above for *E*-**7a** using the known *Z*-iodide[71] (4.10 g, 74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.0 (s, 6H), 0.9 (s, 9H), 1.98 (s, 3H), 4.53 (d, J=6.73 Hz, 1H), 4.59 (d, J=6.73Hz, 1H), 4.7 (d, J=17.82 Hz, 1H), 4.83 (d, J=17.82 Hz, 1H), 4.84 (s, 1H), 6.4 (s, 1H), 7.3 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, 18.3, 21.9, 25.9, 64.4, 71.2, 86.6, 118.0, 127.2, 127.9, 128.4, 128.5, 128.8, 136.7, 137.6, 165.2, 197.5; IR (film) cm^{-1} 3032, 1694, 1606, 1070.

Enone *E*-**7b**. Prepared as above for *E*-**7a** using the known iodide[70] (5.44 g, 95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.0 (s, 6H), 0.9 (s, 9H), 2.0 (s, 3H), 4.06 (s, 2H), 4.58 (s, 2H), 4.88 (s, 1H), 6.74 (s, 1H), 7.3 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, 16.4, 18.3, 26.0, 67.2, 71.1, 87.2, 116.0, 127.3, 127.9, 128.3, 128.5, 128.7, 137.0, 138.0, 159.6, 198.2; IR (film) cm^{-1} 3031, 1690, 1626, 1109.

Enone *Z*-**7b**. Prepared as above for *E*-**7a** using the known[71] *Z*-iodide (4.70 g, 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.0 (s, 6H), 0.88 (s, 9H), 1.96 (s, 3H), 2.82 (t, J=6.3 Hz, 2H), 3.77 (t, J=6.3 Hz, 2H), 4.56 (d, J=12 Hz, 1H), 4.62 (d, J=12 Hz, 1H), 4.85 (s, 1H), 6.39 (s, 1H), 7.4 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, 18.3, 25.9, 27.7, 37.8, 62.4, 71.1, 86.8, 120.0, 127.1, 127.8, 127.9, 128.3, 128.4, 128.7, 136.7, 137.6, 161.2.

Enone *E*-**8a**. Prepared as above for *E*-**7a** using the known iodide[70] (4.50 g, 92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.9 (s, 9H), 1.36 (d, J=6.9 Hz, 3H), 2.24 (s, 3H), 2.41 (t, J=6.6 Hz, 2H), 3.8 (t, J=6.6 Hz, 2H), 3.94 (q, J=6.9 Hz, 1H), 4.43 (d, J=11.7 Hz, 1H), 4.62 (d, J=11.7 Hz, 1H), 6.48 (s, 1H), 7.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, 18.2, 20.1, 25.9, 44.7, 61.2, 71.8, 81.3, 119.7, 127.7, 127.8, 128.4, 137.8, 159.3, 202.5; IR (film) cm^{-1} 1688, 1462; calcd for $C_{21}H_{34}O_3Si$, C, 69.56; H, 9.45; found, C, 69.27; H, 9.78.

Enone *E*-**8b**. Prepared as above for *E*-**7a** using the known iodide[71] (4.98 g, 87%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.0 (s, 6H), 0.85 (s, 9H), 2.18 (s, 3H), 2.32 (t, J=6.53 Hz, 2H), 3.71 (t, J=6.53 Hz, 2H), 4.56 (d, J=12 Hz, 1H), 4.59 (d, J=12 Hz, 1H), 4.85 (s, 1H), 6.41 (s, 1H), 7.3 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, 18.1, 20.2, 26.0, 44.9, 61.8, 71.3, 86.9, 120.5, 127.2, 127.9, 127.9, 128.3, 128.5, 128.8, 136.8, 137.4, 159.2, 198.1; IR (film) cm^{-1} 1702, 1096; calcd for $C_{26}H_{36}O_3Si$, C, 73.54; H, 8.54; found, C, 73.52; H, 8.50.

Enone *E*-**9a**. Prepared as above for *E*-**7a** using the known iodide[70] (2.42 g, 78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, J=6.72 Hz, 3H), 2.3 (s, 3H), 3.93 (q, J=6.72 Hz, 1H), 4.44 (d, J=11.48 Hz, 1H), 4.56 (d, J=11.48 Hz, 1H), 5.48 (d, J=10.5 Hz, 1H), 5.71 (d, J=17.22 Hz, 1H), 6.44 (dd, J=17.20, 10.5 Hz, 1H), 6.50 (s, 1H), 7.3 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 18.2, 71.9, 81.6, 121.2, 122.0, 127.9, 128.5, 137.8, 140.9, 153.2, 203.5; IR (film) cm^{-1} 1700, 1619, 1447.

Enone *E*-**9b**. Prepared as above for *E*-**7a** using the known iodide[70] (2.96 g, 75%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H), 4.54 (d, J=11.88 Hz, 1H), 4.6 (d, J=11.88 Hz, 1H), 4.86 (s, 1H), 5.43 (d, J=10.5 Hz, 1H), 5.63 (d, J=17.4 Hz, 1H), 6.35 (dd, J=17.4, 10.5 Hz, 1H), 6.43

(s, 1H), 7.3 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 71.2, 87.0, 121.1, 122.5, 127.1, 127.9, 128.4, 128.5, 128.7, 136.6, 137.5, 140.7, 153.4, 199; IR (film) cm^{-1} 1633, 1448, 1066.

Hydrazone *E*-**10a**. (Method A) A solution of enone *E*-**7a** (2.0 g, 5.7 mmol) and tosyl hydrazide (1.4 g, 7.5 mmol) in $Ti(OiPr)_4$ (3 mL, 11.5 mmol) was stirred for 16 h at rt. The reaction mixture was then treated with water (10 mL) and the crude product isolated by extractive work-up. The product was recrystallized from ether to provide hydrazone *E*-**10a** (2.12 g, 72%) as colorless crystals, m.p. 85-87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.1 (s, 6H), 0.92 (s, 9H), 1.22 (d, J=6.6 Hz, 3H), 1.54 (s, 3H), 2.33 (s, 3H), 4.1 (m, 5H), 5.8 (s, 1H), 7.12 (d, J=7.2 Hz, 2H), 7.28 (m, 5H), 7.84 (d, J=7.2 Hz, 2H), 7.85 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, 16.3, 18.3, 18.9, 21.5, 25.9, 66.1, 70.3, 78.1, 110.5, 127.5, 127.6, 128.0, 128.3, 129.6, 135.3, 137.9, 144.2, 148.4, 156.9; IR (film) cm^{-1} 3192, 1599, 1451, 1344, 1169; calcd for $C_{27}H_{40}N_2O_4SSi$, C, 62.75; H, 7.80; N, 5.42; found, C, 62.83; H, 7.92; N, 5.33.

Hydrazone *E*-**10b**. Prepared by Method A as above for *E*-**10a** (2.80 g, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.83 (s, 9H), 1.23 (s, 3H), 2.39 (s, 3H), 3.97 (s, 2H), 4.37 (d, J=16.90 Hz, 1H), 4.40 (d, J=16.90 Hz, 1H), 5.07 (s, 1H), 5.59 (s, 1H), 7.28 (m, 12H), 7.7 (s, 1H), 7.81 (d, J=8.32 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, 14.3, 16.2, 18.3, 21.7, 22.8, 25.9, 31.7, 66.1, 70.6, 83.7, 110.5, 126.2, 127.5, 127.6, 128.1, 128.2, 128.4, 129.7, 132.8, 138.0, 138.3, 144.1, 148.6, 156.48; IR (film) cm^{-1}, 3191, 1659, 1598, 1453, 1343, 1169; calcd for $C_{32}H_{42}N_2O_4SSi$, C, 66.40; H, 7.31; N, 4.84; found, C, 66.48; H, 7.44; N, 4.84.

Hydrazone *Z*-**10b**. Prepared as above using Method A for *E*-**10a** (2.14 g, 65%); m.p. 97-99 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.0 (s, 6H), 0.88 (s, 9H), 1.82 (s, 3H), 2.47 (s, 3H), 3.49 (d, J=12.3 Hz, 1H), 3.6 (d, J=12.3 Hz, 1H), 4.39 (d, J=11.7 Hz, 1H), 4.45 (d, J=11.7 Hz, 1H),

5.08 (s, 1H), 5.24 (s, 1H), 7.3 (m, 12H), 7.85 (d, J=8.4 Hz, 2H), 7.93 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, 18.3, 20.7, 21.6, 25.9, 63.2, 70.7, 83.6, 112.9, 126.3, 127.6, 127.7, 128.0, 128.1, 128.3, 129.6, 135.7, 137.7, 138.1, 143.9, 148.5, 154.72; IR (film) cm^{-1}, 3203, 3032, 1648, 1453, 1342, 1168; calcd for $C_{32}H_{42}N_2O_4SSi$, C, 66.40; H, 7.31; N, 4.84; found, C, 66.13; H, 7.29; N, 5.02.

Hydrazone *E*-**11a**. Prepared as above using Method A for *E*-**10a** (2.14 g, 71%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.1 (s, 6H), 0.88 (s, 9H), 1.23 (d, J=6.3 Hz, 3H), 1.58 (s, 3H), 2.32, (t, J=6 Hz, 2H), 2.35 (s, 3H), 3.77 (t, J=6 Hz, 2H), 4.07 (d, J=11.7 Hz, 1H), 4.09 (q, J=6.6 Hz, 1H), 4.14 (d, J=11.7 Hz, 1H), 5.43 (s, 1H), 7.12 (d, J=7.2 Hz, 2H), 7.28 (m, 5H), 7.8 (s, 1H), 7.84 (d, J=7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, 18.3, 18.8, 19.5, 22.6, 26.0, 42.2, 60.9, 70.4, 78.1, 113.9, 127.6, 128.0, 128.3, 129.5, 135.6, 138.0, 144.0, 147.2, 156.1; IR (film) cm^{-1} 3203, 1598, 1458, 1343, 1167.

Hydrazone *E*-**11b**. Prepared as above using Method A for *E*-**10a** (2.12 g, 63%); m.p. 63-65 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.28 (s, 3H), 2.23 (t, J=6.3 Hz, 2H), 2.39 (s, 3H), 3.65 (t, J=6.3 Hz, 2H), 4.4 (d, J=12 Hz, 1H), 4.46 (d, J=12 Hz, 1H), 5.11 (s, 1H), 5.27 (s, 1H), 7.28 (m, 12H), 7.6 (s, 1H), 7.84 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, 18.3, 19.4, 21.6, 26.0, 42.1, 61.0, 70.6, 83.5, 113.8, 126.3, 127.4, 127.6, 128.0, 128.3, 129.5, 135.6, 137.9, 138.2, 144.0, 147.4, 155.6; IR (film) cm^{-1} 3201, 1649, 1453, 1340, 1168; calcd for $C_{33}H_{44}N_2O_4SSi$, C, 66.85; H, 7.48; N, 4.73; found, C, 66.99; H, 7.45; N, 4.90.

Hydrazone *Z*-**11b**. Prepared as above using Method A for *E*-**10a** (1.55 g, 46%); m.p. 106-108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.1 (s, 6H), 0.92 (s, 9H), 1.69 (m, 2H), 1.78 (s, 3H),

2.47 (s, 3H), 3.43 (m, 2H), 4.4 (d, J=8.7 Hz, 1H), 4.49 (d, J=8.7 Hz, 1H), 5.09 (s, 1H), 5.30 (s, 1H), 7.3 (m, 12H), 7.85 (d, J=7.2 Hz, 2H), 8.34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, 18.5, 21.6, 22.6, 26.2, 36.6, 60.3, 70.6, 84.0, 114.9, 126.3, 127.5, 127.6, 128.0, 128.3, 129.5, 135.9, 137.9, 138.4, 143.8, 146.7, 154.5; IR (film) cm^{-1} 3197, 3032, 1650, 1452, 1344, 1168.

Hydrazone *E*-**12a**. Prepared as above using Method A for *E*-**10a** (1.13 g, 50%); m.p. 70-72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, J=6.6 Hz, 3H), 1.76 (s, 3H), 2.38 (s, 3H), 4.1 (d, J=12 Hz, 1H), 4.17 (d, J=12 Hz, 1H), 5.31 (d, J=10.5 Hz, 1H), 5.44 (d, J=17.1 Hz, 1H), 5.62 (s, 1H), 6.43 (dd, J=17.10, 10.5 Hz, 1H), 7.13 (d, J=8.1 Hz, 2H), 7.3 (m, 5H), 7.63 (s, 1H), 7.85 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0, 18.9, 21.5, 70.5, 78.1, 117.6, 127.7, 128.0, 128.3, 129.6, 135.3, 137.8, 138.5, 144.2, 144.9, 155.71; IR (film) cm^{-1}, 3201, 1600, 1449, 1342, 1166; calcd for $C_{22}H_{26}N_2O_3S$, C, 66.30; H, 6.58; N, 7.03; found, C, 66.05; H, 6.56; N, 7.07.

Hydrazone *E*-**12b**. Prepared as above using Method A for *E*-**10a** (1.75 g, 67%); m.p. 115-117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 3H), 2.44 (s, 3H), 4.39 (d, J=11.88 Hz, 1H), 4.45 (d, J=11.88 Hz, 1H), 5.12 (s, 1H), 5.19 (d, J=10.69 Hz, 1H), 5.28 (d, J=17.28 Hz, 1H), 5.43 (s, 1H), 6.28 (dd, J=17.28, 10.69 Hz, 1H), 7.3 (m, 12H), 7.71 (s, 1H), 7.83 (d, J=8.32 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 21.7, 70.8, 83.7, 117.4, 117.6, 126.3, 127.6, 127.8, 128.2, 128.2, 128.47, 129.7, 135.5, 137.8, 138.1, 138.6, 144.3, 145.1, 155.4; IR (film) cm^{-1} 3194, 1599, 1341, 1167; calcd for $C_{27}H_{28}N_2O_3S$, C, 70.41; H, 6.13; N, 6.08; found, C, 70.56; H, 6.13; N, 6.10.

O-Benzylbenzoin (**13**). To a stirred solution of amide **5b** (1.00 g, 3.53 mmol) in ether (9 mL) at -78 °C, phenyllithium (4.91 mL, 8.83 mmol) was added dropwise. Completion of the reaction was monitored by TLC. Then the reaction mixture was allowed to warm to room

temperature and quenched with acetic acid. Extractive work up followed by flash chromatography over silica gel with 5/95 ethyl acetate/hexane provided ketone (0.87 g, 82 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (s, 2H), 5.65 (s, 1H), 7.36 (m, 13 H), 7.98 (d, J=Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.0, 83.4, 127.0, 128.0, 130.0, 134.0; IR (film) cm^{-1} 3061, 2360, 1688, 1449, 1100, 695; calcd for $C_{21}H_{18}O_2$ C, 83.42, H, 6.00; found C, 83.22, H, 5.88.

O-Benzylbenzoin hydrazone *E*-**14**. Method A: Tosyl hydrazide (0.605 g, 3.21 mmol) and titanium(IV) isopropoxide (1.971 g, 2.03 mL, 7.89 mmol) were added to the *O*-benzyl-benzoin (0.60 g, 1.98 mmol). The reaction mixture was stirred at room temperature for 48 h. The reaction mixture was quenched by adding water followed by extractive work up. *E*-hydrazone and *Z*-hydrazone were isolated by flash chromatography over silica gel using 6/94 ethyl acetate/hexane to provide *E*-**14** (0.93 g, 62%). m.p. 166-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 4.51 (s, 2H), 5.36 (s, 1H), 6.74 (d, *J*= 7.66, 2H), 7.27 (m, 15 H), 7.80 (d, *J*=8.10, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 70.8, 83.6, 126.5, 127.4, 128.1, 128.4, 129.1, 129.6, 130.1, 135.3, 137.6, 144.2, 156.9; IR (film) cm^{-1} 3224, 3060, 2918, 1602, 1357, 1166, 1085; calcd for $C_{28}H_{26}N_2O_3S$ C, 71.46, H, 5.57, N, 5.95; found C, 71.27, H, 5.59, N, 6.01.

Method B: A microwave reaction of *O*-benzylbenzoin (0.10 g, 0.33 mmol) with tosylhydrazide (0.074 g, 0.39 mmol) in CH_2Cl_2 (0.5 mL) for 8 h at 30 watts at 30 °C gave a mixture of *E*-hydrazone and *Z*-hydrazone. Flash chromatography over silica gel with 6/94 ethyl acetate/hexane provided 7.25:1 of *E*-**14** and *Z*-**14** hydrazones (0.15 g, 99%).

O-Benzylbenzoin hydrazone *Z*-**14.** Method C: A solution of tosyl hydrazide (0.074 g, 0.39 mmol) and *O*-benzylbenzoin (0.108 g, 0.35 mmol) in MeOH was stirred at 50 °C for 12-28 h. The precipitate was removed by filtration to provide hydrazone *Z*-**14** (0.11 g, 60%) which was

used without further purification. M.p. 166-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 4.44 (d, J= 9.24), 4.55 (d, J=9.24), 5.73 (s, 1H), 7.30 (m, 15H), 7.72 (d, J=8.96, 2H), 10.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 28.1, 71.8, 80.4, 126.4, 127.4, 127.8, 128.1, 128.5, 128.9, 129.6, 135.13, 136.24; IR (film) cm^{-1} 3200, 3027, 1347, 1164; calcd for $C_{28}H_{26}N_2O_3S$ C, 71.46, H, 5.57, N, 5.95; found C, 71.34, H, 5.63, N, 6.01.

1,4-*syn*-*E*-Alkene **22a**. (Method A) Catecholborane (0.22 mL, 2.3 mmol) was added dropwise to a mixture of hydrazone *E*-**10a** (0.20 g, 0.39 mmol) and silica gel (0.40 g) in $CHCl_3$ (5 mL) at -42 ^{0}C. After 1 h at -42 ^{0}C, NaOAc trihydrate (0.79 g, 5.8 mmol) was added and the reaction mixture was heated under reflux for 16 h. The reaction mixture was poured into water and isolated by extractive work-up. The crude material was purified by flash chromatography over silica gel with 5/95 ethyl acetate/hexane to give *syn*-**22a** (0.12 g, 92%) as colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.92 (s, 9H), 1.07 (d, J=6.6 Hz, 3H), 1.32 (d, J=6.3 Hz, 3H), 2.39 (m, 1H), 3.51 (qd, J=9.6, 6.6 Hz, 2H), 3.92 (m, 1H), 4.4 (d, J=12 Hz, 1H), 4.59 (d, J=12 Hz, 1H), 5.45 (dd, J=15.6, 7.5 Hz, 1H), 5.61 (dd, J=15.6, 6.9 Hz, 1H), 7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.0, 16.6, 18.3, 21.8, 25.9, 39.0, 68.0, 69.6, 75.9, 127.3, 127.7, 128.3, 131.5, 135.7, 139.1; IR (film) cm^{-1} 3032, 1689, 1626, 1453, 1110; calcd for $C_{20}H_{34}O_2Si$, C, 71.80; H, 10.24; found, C, 72.04; H, 10.38.

(Method B) To a mixture of hydrazone *E*-**10a** (0.40 g, 0.78 mmol) and CH_3CO_2H (0.35 mL, 6.14 mmol) in freshly distilled $CHCl_3$ (9.8 mL), catecholborane (0.25 mL, 2.303 mmol) was added dropwise at -42 °C. After 4 h, $NaOAC.3H_2O$ (1.566 g, 11.51 mmol) was added and the reaction mixture was heated to 55 °C for 16 h. After completion of the reaction, the mixture was poured into water and extracted with ether. The crude material was purified by flash

chromatography over silica gel with 5/95 ethyl acetate/hexane to obtain pure alkene *syn*-**22a** as colorless oil (0.22 g, 85%); 0.04 g scale reaction (0.025 g, 98%); 0.10 g scale reaction (0.06 g, 92%).

1,4-*syn*-*E*-Alkene **22b**. Prepared as above for *syn*-**22a**, using Method A, (0.07 g, 88%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.01(s, 3H), 0.86 (s, 9H), 1.01 (d, J=6.78 Hz, 3H), 2.35 (m, 1H), 3.42 (dd, J=9.68, 6.63 Hz, 1H), 3.48 (dd, J=9.68, 6.43 Hz, 1H), 4.48 (d, J=12.03 Hz, 1H), 4.53 (d, J=12.12 Hz, 1H), 4.79 (d, J=5.85 Hz, 1H), 5.61(dd, J=15.53, 5.95 Hz, 1H), 5.68 (dd, J=15.48, 5.84 Hz, 1H), 7.30 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, 16.5, 18.0, 26.0, 39.13, 67.9, 69.9, 81.9, 127.0, 127.5, 127.8, 128.4, 128.4, 128.5, 130.3, 136.3, 138.7, 141.7; IR (film) cm^{-1} 3100, 1635, 1096; calcd for $C_{25}H_{36}O_2Si$, C, 75.70; H, 9.15; found C, 75.87; H, 9.32.

1,4-*anti*-*E*-Alkene **22b**. Prepared as above using Method A for *syn*-**22a** (0.067 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.87 (s, 9H), 0.98 (d, J=6.6 Hz, 3H), 2.37 (m, 1H), 3.46 (m, 2H), 4.48 (d, J=12 Hz, 1H), 4.52 (d, J=12 Hz, 1H), 4.79 (d, J=5.54 Hz, 1H), 5.64 (m, 2H), 7.3 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, 16.4, 18.4, 26.0, 39.1, 68.0, 69.9, 81.8, 127.0, 127.5, 127.8, 128.4, 128.4, 130.3, 136.4, 138.7, 141.7; calcd for $C_{25}H_{36}O_2Si$, C, 75.70; H, 9.15; found, C, 75.73; H, 9.30.

1,4-*syn*-*E*-Alkene **26a**. Prepared as above for *syn*-**22a**, using Method A (0.06 g, 85%); Method B (0.056 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.94 (s, 9H), 1.07 (d, J=6.9 Hz, 3H), 1.31 (d, J=6.3 Hz, 3H), 1.58 (m, 2H), 2.39 (m, 1H), 3.64 (m, 2H), 3.92 (m, 1H), 4.4 (d, J=12 Hz, 1H), 4.59 (d, J=12 Hz, 1H), 5.4 (dd, J=15.6, 7.2 Hz, 1H), 5.53 (dd, J=15.6, 7.5 Hz, 1H), 7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.0, 18.3, 20.8, 21.9, 26.0, 32.9, 39.7,

61.3, 69.6, 75.8, 127.3, 127.7, 128.3, 130.5, 138.7, 139.0; IR (film) cm^{-1} 3100, 1460, 1098; calcd for $C_{21}H_{36}O_2Si$, C, 72.35; H, 10.41; found, C, 72.27; H, 10.48.

1,4-*syn*-*E*-Alkene **26b**. Prepared as above using Method A for *syn*-**22a**, (0.068 g, 83%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.01(s, 3H), 0.88 (s, 9H), 1.08 (d, J=6.9 Hz, 3H), 1.54 (m, 2H), 2.35 (m, 1H), 3.57 (m, 2H), 4.52 (d, J=12 Hz, 1H), 4.56 (d, J=12 Hz, 1H), 4.8 (m, 1H), 5.59 (m, 2H), 7.30 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, 18.3, 20.5, 25.9, 33.0, 39.6, 61.2, 69.8, 81.7, 126.8, 127.4, 127.7, 128.3, 128.4, 129.3, 138.6, 139.1, 141.8; IR (film) cm^{-1} 3100, 1636, 1096.

1,4-*anti*-*E*-Alkene **26b**. Prepared as above using Method A for *syn*-**22a** (0.065 g, 80%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.03 (d, J=6.9 Hz, 3H), 1.57 (m, 1H), 2.37 (m, 1H), 3.65 (m, 2H), 4.52 (d, J=12 Hz, 1H), 4.58 (d, J=12 Hz, 1H), 4.82 (m, 1H), 5.62 (m, 2H), 7.3 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, 18.3, 20.3, 26.0, 32.9, 39.7, 61.3, 69.9, 81.6, 126.8, 127.4, 127.7, 128.3, 128.4, 129.2, 138.7, 139.1, 141.8; IR (film) cm^{-1} 3100, 1636, 1097; calcd for $C_{26}H_{38}O_2Si$, C, 76.04; H, 9.33; found, C, 76.21; H, 9.57.

1,4-*syn*-*E*-Alkene **27a**. Prepared as above using Method A for *syn*-**22**, (0.035 g, 81%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, J=6.9 Hz, 3H), 1.30 (d, J=6.3 Hz, 3H), 2.91 (m, 1H), 3.92 (m, 1H), 4.39 (d, J=12 Hz, 1H), 4.57 (d, J=12 Hz, 1H), 5.0 (d, J=10.2 Hz, 1H), 5.04(d, J=17.4 Hz, 1H), 5.4 (dd, J=15.6, 7.8 Hz, 1H), 5.6 (dd, J=15.6, 6.6 Hz, 1H), 5.82 (m, 1H), 7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 21.8, 39.9, 69.7, 75.7, 113.1, 127.3, 127.7, 128.3, 130.8, 136.6, 142.5.

1,4-*syn*-*E*-Alkene **27b**. Prepared as above for *syn*-**22a**, using Method A (0.053 g, 95%; Method B (0.050 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, J=6.9 Hz, 3H), 2.95 (m, 1H), 4.55 (d, J=12 Hz, 1H), 4.59 (d, J=12 Hz, 1H), 4.88 (d, J=6 Hz, 1H), 5.00 (d, J=10.2 Hz, 1H), 5.04 (d, J=17.4 Hz, 1H), 5.7 (m, 2H), 5.84 (m, 1H), 7.30 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 40.0, 69.9, 81.6, 113.3, 126.9, 127.5, 127.7, 128.4, 128.4, 129.7, 137.1, 138.6, 141.7, 142.4; calcd for $C_{20}H_{22}O$, C, 86.29; H, 7.97; found, C, 86.16; H, 8.14; IR (film) cm^{-1} 3030, 1643, 1453, 1064.

Determination of Relative Configuration of *syn*-**22a**: A solution of 1,4-*syn* alkene **22a** (0.096 g, 0.24 mmol) and NBu_4F (0.25 mL, 1M in THF, 0.25 mmol) in THF (1 mL) was stirred for 8 h. After extractive work-up, the crude material was purified by flash chromatography over silica gel with 15/85 ethyl acetate/hexane to give alcohol **23a** (0.050 g, 95%) as colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (d, J=6.6 Hz, 3H), 1.31 (d, J=6.3 Hz, 3H), 2.41 (m, 1H), 3.45 (dd, J=10.5, 7.2 Hz, 1H), 3.52 (dd, J=10.8, 6.0 Hz, 1H), 3.94 (m, 1H), 4.42 (d, J=12 Hz, 1H), 4.63 (d, J=12 Hz, 1H), 5.54 (m, 2H), 7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 21.7, 39.3, 67.2, 69.8, 75.6, 127.4, 127.7, 128.4, 133.1, 134.8, 138.8.

Alcohol **23a** (0.079 g, 0.36 mmol), Pd/C (38 mg, 10 wt. % on activated carbon, 0.036 mmol) and methanol (2 mL) was added to a Parr bottle. The reduction was performed under a H_2 atmosphere at 70 psi for 2 h. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The crude material was purified by flash chromatography over silica gel with 50/50 ethyl acetate/hexane to give the diol (0.042 g, 95%).

Jones reagent (0.13 mL, 2.67 N in H_2SO_4, 0.36 mmol) was added dropwise over 5 min at 0 °C to a solution of the diol (0.042 g, 0.32 mmol) in acetone. The mixture was allowed to warm

to rt and stirred for 1h. After extractive work-up, the crude material was purified by flash chromatography over silica gel with 1/99 ethyl acetate/hexane to give *cis*-2-methyl-5-hexanolide **24** (0.012 g, 30%). All spectroscopic data were in agreement with reported data.[61]

Determination of enantiomer ratio of *syn*-**22a**: Mosher ester (*S*)-**25a**.[72] A solution of alcohol **23a** (0.017 g, 0.08 mmol)**,** (*S*)-(-)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (23.5 mg, 0.09 mmol), NEt_3 (14 μL, 0.1 mmol) and DMAP (catalytic amount) in CH_2Cl_2 (1 mL) stirred for 2 h, then isolated by extractive work-up. The crude material was purified by flash chromatography over silica gel with 5/95 ethyl acetate/hexane to give Mosher ester (*S*)-**25a** (0.033 g, 95%) as colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, J=6.9 Hz, 3H), 1.25 (d, J=6.3 Hz, 3H), 2.65 (m, 1H), 3.56 (s, 3H), 3.87 (m, 1H), 4.18 (dd, J=10.5, 6.3 Hz, 1H), 4.28 (dd, J=10.5, 6.6 Hz, 1H), 4.36 (d, J=12 Hz, 1H), 4.53 (d, J=12 Hz, 1H), 5.52 (m, 2H), 7.25-7.60 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 21.5, 35.6, 55.4, 69.8, 70.4, 75.5, 127.4, 127.6, 128.3, 128.4, 129.6, 133.1, 133.2.

Mosher ester (*R*)-**25a**. Prepared as above using (*R*)-(-)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (d, J=6.6 Hz, 3H), 1.24 (d, J=6.3 Hz, 3H), 2.64 (m, 1H), 3.57 (s, 3H), 3.87 (m, 1H), 4.22 (dd, J=12.9, 6.6 Hz, 1H), 4.25 (dd, J=10.5, 6.6 Hz, 1H), 4.36 (d, J=12 Hz, 1H), 4.52 (d, J=12 Hz, 1H), 5.50 (m, 2H), 7.25-7.60 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 21.5, 35.7, 55.4, 69.8, 70.3, 75.5, 127.4, 127.6, 128.3, 128.4, 129.6, 133.1, 133.2.

Determination of enantiomer ratio of *syn*-**22b**: Desilylated alcohol **23b** was prepared as above for **23a** (0.067 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J=6.6 Hz, 3H), 2.25 (m, 1H), 3.38 (m, 2H), 4.34 (s, 2H), 4.77 (d, J=6.6 Hz, 1H), 5.44 (dd, J=15.6, 7.2 Hz, 1H), 5.56 (dd,

J=15.6, 7.2 Hz, 1H), 7.32 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 39.1, 67.0, 69.8, 81.3, 126.7, 127.3, 127.4, 127.5, 128.2, 128.3, 131.7, 134.9, 138.2, 141.2.

Mosher ester (*S*)-**24**. Prepared as above for **25a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, J=6.9 Hz, 3H), 2.64 (m, 1H), 3.46 (s, 3H), 4.21 (m, 2H), 4.49 (s, 2H), 4.79 (d, J=6 Hz, 1H), 5.6 (m, 2H).

Mosher ester (*R*)-**24**. Prepared as above for **25a.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, J=6.9 Hz, 3H), 2.64 (m, 1H), 3.48 (s, 3H), 4.22 (m, 2H), 4.5 (s, 2H), 4.80 (d, J=6 Hz, 1H), 5.67 (m, 2H).

Integration of the OCH_3 peak of the Mosher esters revealed a 2.6-2.9:1 *er* of diastereomers, consistent with the 2.7:1 *er* of Weinreb amides obtained by chiral shift NMR experiment, indicating that no significant racemization had occurred in the conversion of the Weinreb amide to **5b**.

Silyl ether **33**. $LiAlH_4$ (1.52 g, 40.0 mmol) was added slowly to a cooled and stirred solution of β-bromoangelic acid **32**[66] (7.16 g, 40.0 mmol) in THF (85 mL). After 16 h at rt, an additional charge of $LiAlH_4$ (0.152 g, 4.0 mmol) was added. After cooling to 0 °C, excess $LiAlH_4$ was quenched with saturated solution of Na_2SO_4 (2.2 mL). Ether (55 mL) was added, and the mixture poured into 2M H_2SO_4 (80 mL) and the organic layer separated. The aqueous layer was extracted 3 times with CH_2Cl_2. The combined organic layers were concentrated and the remaining oil dissolved in CH_2Cl_2 and washed with 10% aqueous solution of K_2CO_3 (28 mL). The combined organic layers were concentrated and dried in vacuo. The residue was recrystallized from ether to give the corresponding alcohol (4.49 g, 68%). ^{1}H NMR (300 MHz,

$CDCl_3$) δ 1.98 (s, 3H), 2.40 (s, 3H), 4.20 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 25.2, 62.6, 121.8, 133.4.

A solution of the alcohol (1.49 g, 9.05 mmol) in DMF (4.5 mL), TBSCl (1.63 g, 10.86 mmol) and imidazole (0.736 g, 10.86 mmol) was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with hexane to give ether **33** (1.97 g, 78%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.92 (s, 9H), 1.92 (s, 3H), 2.36 (s, 3H), 4.19 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.4, 23.2, 25.7, 29.8, 30.7, 67.6, 81.9, 124.3, 138.8.

Vinyl iodide **34**. A Schlenk tube was evacuated and backfilled with N_2. The tube was charged with CuI (191 mg, 1.0 mmol), NaI (4.5 g, 30 mmol), *N*,*N*-dimethylethylenediamine (213 μL, 2.0 mmol), bromide **33** (5.586 g, 20 mmol) and *n*-BuOH (10 mL) under N_2. The Schlenk tube was sealed with the stopper and the reaction mixture was stirred at 120 °C for 24 hours. The resulting mixture was allowed to cool to room temperature and poured into ethyl acetate (100 mL). The mixture solution was washed with 30% aq NH_4OH (5 mL) in water (100 mL), followed by 3 washes with 100 mL of water. The organic phase was dried with $MgSO_4$ and concentrated in vacuo to give liquid vinyl iodide **34** (5.51 g, 76%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.92 (s, 9H), 1.98 (s, 3H), 2.59 (s, 3H), 4.22 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$)) δ 5.3, 13.7, 18.3, 25.6, 27.0, 29.8, 34.9, 60.8, 62.7, 98.1, 139.8.

Enone **35a.** t-BuLi (13.28 mL, 1.5 M in pentane, 20 mmol) was added slowly to a solution of vinyl iodide **34** (3.263 g, 10 mmol) in ether at –78 °C. After 30 minutes, a solution of amide **5a** (2.22 g, 10 mmol) in ether was added dropwise. After 2 hours, the reaction mixture was quenched with acetic acid at 0 °C. After extractive work up with hexane, crude product was purified by flash chromatography over silica gel with 5/95 ethyl acetate/hexane to give enone

(2.10 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.91 (s, 9H), 1.40 (d, J=6.8 Hz, 3H), 1.56 (s, 3H), 1.83 (s, 3H), 4.20 (s, 2H), 4.28 (m, 1H), 4.49 (d, J=12.8 Hz), 4.67 (d, J=10.8 Hz), 7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 14.7, 17.1, 17.5, 18.3, 25.7, 26.4, 29.7, 63.0, 71.6, 78.6, 127.8, 128.4, 148.5.

Enone 35b. Prepared as above for enone **35a** using amide **5b** (2.71 g, 64 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.91 (s, 10 H), 1.60 (s, 6H), 4.11 (s, 2H), 4.54 (d, J=3.6 Hz, 1H), 4.70 (d, J=3.6 Hz, 1H), 5.17 (s, 1H), 7.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.1, 14.0, 16.9, 18.3, 25.8, 62.1, 70.7, 84.6, 127.9, 128.7, 130.5, 135.6, 137.4, 138.3, 205.3.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Copies of ^{1}H- and ^{13}C-NMR spectra of all new compounds, .xyz files of all calculated structures.

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Notes

The authors declare no competing financial interest.

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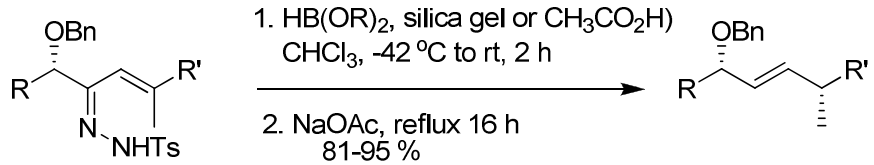
TOC graphic



R= Me, Ph
R'= CH_2OTBS, CH_2CH_2OTBS, $CH{=}CH_2$

(20:1 dr)