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A Convergent Pd-Catalyzed Asymmetric Allylic Alkylation of *dl*- and *meso*-Divinylethylene Carbonate: Enantioselective Synthesis of (+)-Australine Hydrochloride and Formal Synthesis of Isoaltholactone

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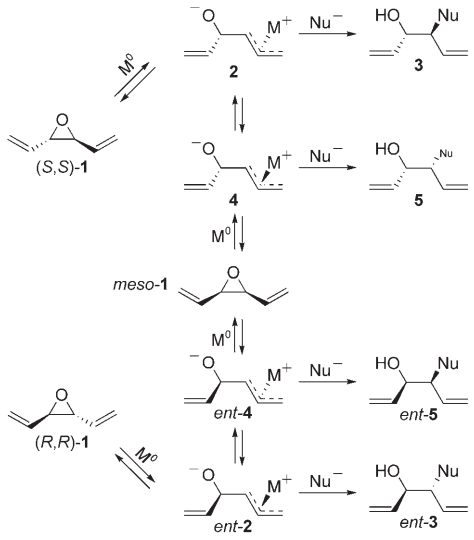
Abstract: The use of a mixture of *dl*- and *meso*-divinylethylene carbonate as an electrophile in palladium-catalyzed asymmetric allylic alkylation reactions is reported. From the diastereomeric mixture of *meso* and chiral racemic starting materials, a single product is obtained in high optical purity employing either oxygen or nitrogen nucleophiles. The resulting dienes have proven to be versatile synthetic intermediates as each carbon is functionalized for further transformation and differentiated by virtue of the reaction. A mechanism for this intriguing transformation is proposed and a concise enantioselective total synthesis of (+)-australine hydrochloride is reported as well as a formal synthesis of isoaltholactone.

Keywords: asymmetric catalysis · asymmetric synthesis · natural products · palladium · total synthesis

Introduction

The development of catalytic asymmetric reactions that use feedstock chemicals, or easily prepared starting materials, to produce functionalized building blocks in high optical purity continues to be at the forefront of modern synthetic organic chemistry. To achieve this goal, our work in the area of palladium-catalyzed asymmetric allylic alkylation (AAA) has focused on exploiting the well-known reaction mechanism by targeting either the ionization or nucleophilic addition steps as enantiodetermining.[1] Based on the successful palladium-catalyzed dynamic kinetic asymmetric transformation (DYKAT) of racemic butadiene monoepoxide,[2] we postulated that a reasonable extension of this chemistry may be realized by the addition of a second vinyl group to the substrate providing a triene monoepoxide (hexatriene monoepoxide **1**, Scheme 1). This structural modification, would theoretically allow for both stereogenic centers to be epimerized by a metal catalyst and by such a mechanism, racemization of the starting material would be possible ((*S*,*S*)-**1** → (*R*,*R*)-**1** via *meso*-**1**). The success of the reaction would then hinge upon the ability of each stereoisomer of the substrate to be efficiently ionized and the resulting π-complexes to equilibrate at appropriate rates. Nucleophilic attack would then selectively provide one enantiomer of one of the diastereomers that could possibly be formed. While triene monoepoxides would be the simplest substrates, in principle any substrate that incorporates a leaving group that may also reversibly add to the π-complex may work in these types of processes.



Scheme 1. Potential DYKAT of triene monoepoxides.

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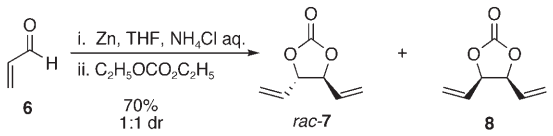
The functionalized dienes produced using heteroatom nucleophiles would be monoprotected diols or N-protected amino alcohols with two adjacent stereocenters set during the reaction. As these compounds would have each atom of the framework differentiated by virtue of the reaction, they should be well suited for further selective transformations and find application in natural product synthesis. Use of these diols in syntheses has recently been reported,[3] but the starting materials are derived from the chiral pool and required multistep preparations.[4] As both enantiomers of product would be available using a catalytic enantioselective approach and the necessary substrates should be easily prepared, we sought to test our hypotheses.

Results and Discussion

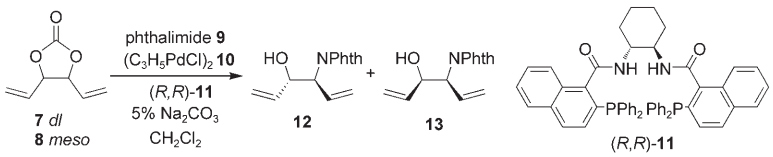
Optimization studies: Upon initial inspection, the parent triene monoepoxide, hexatriene monoepoxide, would seem to be the most atom economic choice of substrate for the reaction. While this epoxide would certainly incorporate all atoms of the starting material into the product, previous reports indicated that it would be difficult to prepare and handle, especially *meso*-**1**.[5] It was postulated that 1,2-divinylethylene carbonate[6] (**7** and **8**) could be employed as a suitable surrogate. Use of the cyclic carbonate would hopefully also function to tether the leaving group to the substrate, a structural feature that is integral to the reversibly epimerizing nature of the necessary intermediates. Furthermore, the carbonate was envisioned to derive readily from a bulk chemical, acrolein (Scheme 2). Reductive dimerization[7] of acrolein **6** with zinc followed by cyclization in neat diethyl carbonate[5a] provided the *dl*- and *meso*-isomers **7** and **8** on a large scale as a 1:1 mixture of separable diastereomers in good yield.



Scheme 2. Preparation of 1,2-divinylethylene carbonate.

Preliminary studies focused on employing phthalimide **9** in the desired reaction. Neglecting the regiochemistry of the nucleophilic addition, the products of the palladium-catalyzed asymmetric allylic alkylation (Pd AAA) of **7** and **8** by the well-established double inversion mechanism[8] would be expected to be diastereomers **12** and **13**, respectively (Table 1). Using initial conditions that functioned well in DYKAT reactions of butadiene monoepoxide as a starting point,[2a] when the *dl*-carbonate **7** was allowed to react with phthalimide in the presence of 5 mol% π-allylpalladium chloride dimer **10**, 15 mol% racemic **11**, and 5 mol% Na_2CO_3 in CH_2Cl_2,[2a] the only product isolated was the expected amino alcohol **12** in 81% yield (entry 1, Table 1).

Table 1. Pd AAA using phthalimide as a nucleophile.



Entry	Carbonate	**10** [mol%][a]	Product	Yield [%][b]	*ee* [%]
1[c]	**7**	5.0[d]	**12**	81	–
2[c]	**7**	5.0	**12**	44 (88)[e]	>99
3[c]	**7**	2.0	**12**	43 (86)[e]	>99
4[c]	**8**	5.0[d]	**12**	71	–
5[c]	**8**	5.0	**12**	74	>99
6[c]	**8**	2.0	**12**	71	>99
7[f]	**7**+**8**[g]	1.0	**12**	74 (99)[e,h]	>99

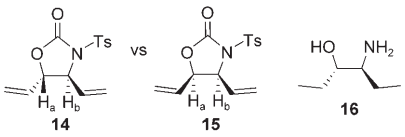
[a] $(C_3H_5PdCl)_2$/**11** 1:3. [b] All yields based on mmol **7** and/or **8**. [c] 0.5 mmol scale, 16 h reaction time with 1.1 equiv **9**. [d] *rac*-**11**. [e] Based on a theoretic maximum for 50% conversion of **7** as discussed below. [f] 5.0 mmol scale, 72 h reaction time with 0.77 equiv **9**. [g] 1:1 mixture **7**:**8**. [h] 16% (*R*,*R*)-**7** was also recovered in 91% *ee*.

Using 5 mol% ligand (*R*,*R*)-**11** and 2 mol% **10** (entries 2, 3), **12** was again isolated as the sole product in >99% *ee* but with 44 and 43% yield, respectively, due to the kinetic resolution of racemic **7** (see below).

The reaction was next attempted with the cyclic carbonate **8** (entries 4–6) to determine how well the catalyst system would work with an acyclic bisallylic *meso* compound, a class of substrates that has not been explored in intermolecular Pd AAA reactions.[9] To our delight, using both racemic **11** and (*R*,*R*)-**11** the *only* product formed was the *syn*-diastereomer **12** (entries 4 and 5). In both reactions the yield was acceptable and in entry 5 the *ee* was >99%. The catalyst loading could also be reduced (2 mol% **10**, entry 6) while both the yield and *ee* were maintained. These results provided preliminary evidence that a mechanistic scenario such as that illustrated in Scheme 1 could be entered into from at least two of the three substrates.

In an attempt to render this a high throughput process, and since **7** and **8** are prepared in the same reaction and both exclusively gave product **12** with excellent *ee*, the reaction was carried out on a 1:1 mixture of **7** and **8** obtained from **6**. Under optimized conditions with prolonged reaction time, the process performed equally well giving **12** with >99% *ee* using 1 mol% **10** in 74% yield (based on charged **7**+**8**) wherein the maximum theoretical yield is 75%. Interestingly, the cyclic carbonate (*R*,*R*)-**7**, recovered in 16% yield (theoretical max. 25%), has a 91% *ee*, indicative of a kinetic resolution of racemic **7** present in the starting material by the chiral catalyst system.

The relative configuration of **12** was initially determined by conversion to the corresponding *N*-tosyl-oxazolidinone and comparison to the known *cis*- and *trans*-*N*-tosyl-oxazolidinones (**14** and **15**). Both compounds had been previously prepared and demonstrate suitably different chemical shifts for the labeled protons (δ H_a/H_b in **14** = 4.54, 4.53 ppm versus δ H_a/H_b in **15** = 5.08, 4.93 ppm) that allowed for facile identification.[10] The absolute configuration was later determined to be *S*,*S* by conversion to the known saturated



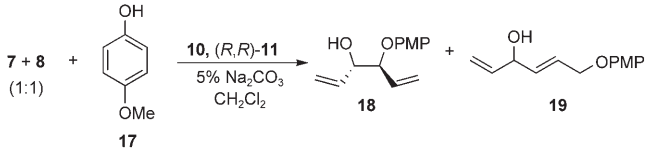
14 15 16

amino alcohol **16**[11] and comparison of the sign of the observed optical rotation $[\alpha]_D^{25} = -23.2$ ($c = 0.8$, MeOH) to the reported value $[\alpha]_D^{23} = -16.9$ ($c = 0.8$, MeOH).[12]

To probe the robustness of our system and explore the scope of the reaction for future synthetic purposes, the use of oxygen nucleophiles was explored in an effort to produce monoprotected 1,2-diols. Initial efforts focused on using easily deprotected simple alcohols such as *p*-methoxybenzyl alcohol. Unfortunately, all attempts to use the alcohol in the presence or absence of boron co-catalyst[2b,13] failed. Additionally, the stoichiometric use of borates,[2b] zinc alkoxides,[14] or inorganic carbonate[15] also failed to provide any of the desired product.

Phenols represent another class of oxygen nucleophiles that have been successfully employed in asymmetric allylic alkylation reactions. Since *p*-methoxyphenol can be deprotected by oxidative means, its use was explored and this alcohol provided the first promising results, as seen in Table 2.

Table 2. Pd AAA using *p*-methoxyphenol as a nucleophile.



17 18 19

Entry[a]	18/19	Entry[a]	18/19
1[b]	1.5:1	6[g]	1:2
2[c]	1.3:1	7[h]	1.7:1
3[d]	1.2:1	8[i,j]	2.3:1
4[e]	–	9[i,k]	2.3:1
5[f]	1.3:1		

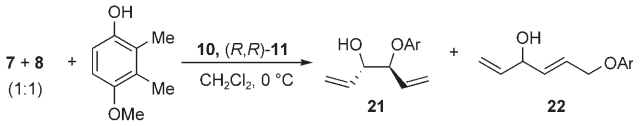
[a] Reactions carried out under N_2 with 1.1 equiv **17**, 2.5 mol% $(C_3H_5PdCl)_2$, and 7.0 mol% **11**. [b] *Rac*-**11**; **18** + **19** obtained in 69% combined yield. [c] (*R*,*R*)-**11**; **18** + **19** obtained in 59% combined yield with **18** in 99% *ee*. [d] *dl*-isomer only. [e] 2 equiv **17**, 2 equiv AcOH (no Na_2CO_3); only trace products. [f] 5.0 mol% Et_3B added. [g] 1 equiv Et_3B added. [h] $T = 0 \rightarrow 4$ °C, 0.8 equiv **17**. [i] **17** added over 5 h [j] T 0 °C. [k] No base added, $T = 0$ °C → ambient. PMP = *p*-methoxyl.

Employing racemic naphthyl ligand under standard conditions, alkylated product was obtained in a combined yield of nearly 70% of a 1.5:1 ratio of branched to linear regioisomers (entry 1). While this ratio leaves much to be desired, it is important to note that only one diastereomer of the branched isomer **18** was obtained. The *syn* stereochemistry is assigned in analogy to results that will be discussed below. When (*R*,*R*)-naphthyl ligand was employed, a slightly worse regioisomeric ratio was observed in 59% yield, but importantly the branched isomer was obtained in 99% *ee*. Several sets of conditions were tried, but were met with limited success.

These results seemed to indicate that the rate of nucleophilic attack needed to be slowed to favor alkylation of one specific π-allylpalladium complex. If the reaction is believed to involve a kinetic resolution of the *rac*-**7** and complete reaction of *meso*-**8**, then only 75% of the starting material will react. In an attempt to slow the rate of the nucleophilic attack, a series of systematic changes of conditions was performed. The concentration of the reaction was decreased to 0.1 M, the amount of nucleophile decreased to 0.8 equiv (75% required for all starting material to react, 5% to form the active catalyst), the temperature lowered to 0 °C, the phenol added over 5 h via syringe pump, and base was omitted from the reaction mixture. These changes increased the ratio to 2.3:1—only a modest change, but nevertheless in the correct direction.

Another way to potentially slow the rate of nucleophilic attack is to increase the steric hinderance of the nucleophile and led to an examination of other types of substituted phenols. The nucleophile **20** was designed to contain an *ortho*-methyl group to slow down the nucleophilic attack and also a *p*-methoxy group so oxidative deprotection of the product could be effected. Under fairly standard conditions, with 2.5 mol% allylpalladium chloride dimer and 7.0 mol% racemic naphthyl ligand at 0 °C, 0.1 M in CH_2Cl_2 the regioisomers **21** and **22** were obtained in a 7.5:1 ratio in 77% yield (Table 3, entry 1). The ratio obtained using **20** is a substantial improvement over that observed using *p*-methoxyphenol **17** (see Table 2, entry 1). Using (*R*,*R*)-**10**, **21** and **22** were obtained in 53% yield as an 8.9:1 ratio with 98% *ee* for **21** (Table 3, entry 2). Decreasing the amount of phenol to 0.8 equivalents increased the ratio to 10.3:1, with a similar chemical yield (entry 3). In an attempt to increase the mass recovery, the reaction was run under an atmosphere of carbon dioxide. As listed in entry 4 (Table 3) this modification did not increase the yield and decreased the ratio of regioisomers. On larger scale with decreased catalyst loading (entry 5) and prolonged reaction time (72 h), a 64% yield of a 12:1 ratio was obtained providing the branched isomer **21** with 98% *ee*. The increased chemical yield and the ratio of

Table 3. Pd AAA using phenol **20** as a nucleophile.



20 21 22

Entry	10 [%][a]	Equiv 20	21/22	Yield 21+22 [%]	21 *ee* [%]
1	2.5[b]	1.1	7.5:1	77	98
2	2.5	1.1	8.9:1	53 (71)[c]	98
3	2.5	0.8	10.3:1	55 (73)	98
4[d]	2.5	0.8	7.3:1	54 (72)	98
5[e]	1.0	0.77	12:1	64 (85)	98

[a] Reactions carried out under an atmosphere of N_2 for 16 h using $(C_3H_5PdCl)_2$/**11** 1:3. [b] *rac*-**11**, ambient temperature. [c] Based on 75% maximum yield as discussed below. [d] CO_2 atmosphere. [e] 72 hour reaction time.

regioisomers were deemed a satisfactory result. The *ee* of the linear compound could not be determined by HPLC analysis, although the optical rotation was nearly zero.

Since addition of the 2,3-dimethyl groups drastically increased the ratio of observed regioisomers, it was postulated that further increasing the steric bulk of the *ortho* group may increase the ratio even further. To this end, the 2-*tert*-butyl-4-methoxyphenol was utilized. Unfortunately, under the standard reaction conditions only a 1:1 ratio of branched to linear product was observed. It seems that when the *ortho* group is too sterically bulky, that nucleophilic addition to the internal carbon is slowed and alkylation at the terminal carbon is increased.

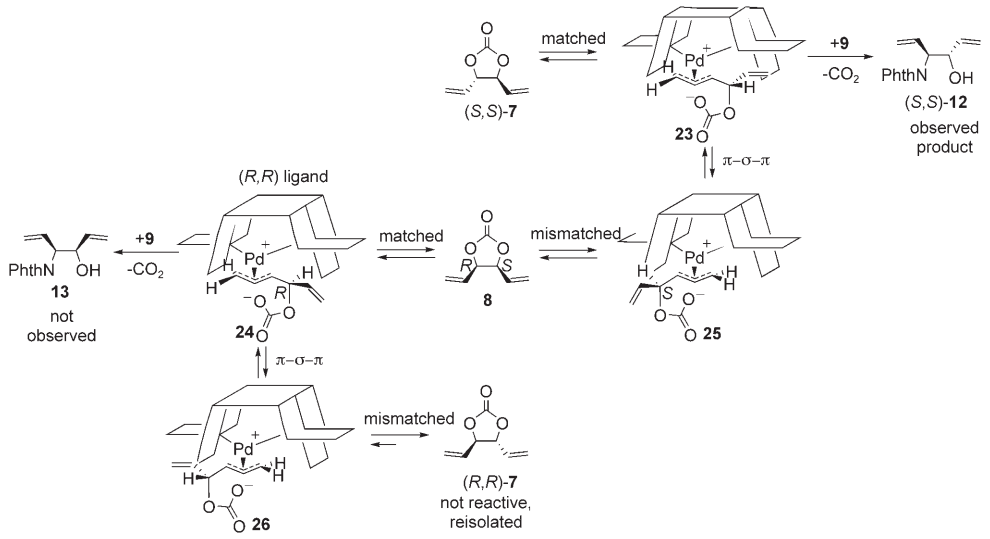
To determine the relative and absolute configuration, we sought to deprotect the aryl group to unmask the corresponding diol which would either be *meso* or one of the *dl* isomers whose rotations are known. Treatment of **21** with ceric ammonium nitrate in the mixed acetonitrile/water solvent system gave a quinone monoketal in nearly quantitative yield. Hydrolysis, although sluggish, provided a sample of the corresponding diol whose absolute configuration was determined to be *S*,*S* by comparison of optical rotation of our synthetic material {$[\alpha]_D^{22} = +82.6$ ($c = 0.66$, EtOH)} to the known sugar derived material{$[\alpha]_D^{25} = -79.3$ ($c = 0.64$, EtOH)}.[4a]

Mechanism: The methodology presented not only provides products useful for synthetic purposes, but is intriguing from a mechanistic standpoint also. Previously, either the ionization or nucleophilic addition steps of the mechanism were exploited independently as the enantiodetermining step. Typically, different conditions are designed to either favor rapid nucleophilic addition to the initially formed π-allylpalladium complex or to promote equilibration of diastereomeric complexes. Under ideal conditions, coupling these pathways may theoretically provide a suitable manifold for both overall retention and inversion of product stereochemistry and thus a convergent pathway emanating from different substrates may arise. The conditions necessary for this type of process to occur must achieve a delicate balance between the relative rates of equilibration and nucleophilic addition. Based on the results outlined in Table 1, both types of enantiodiscrimination are postulated to be occurring in the present study.

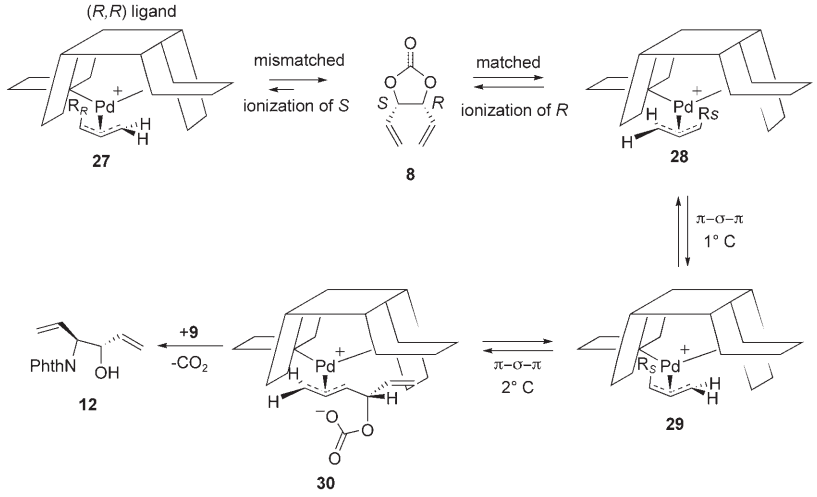
Using the (*R*,*R*)-naphthyl ligand, the *S*,*S* product is obtained from both *dl*- and *meso*-carbonates **7** and **8** (Scheme 3). This interesting result raises questions about how the *dl* and *meso* compounds are converted to the same product and what the origin of the enantioselectivity is. As was previously reported, a mechanism involving all-*syn*-π-allylpalladium complexes is possible (Scheme 3).[16] Using the familiar wall and flap diagram to represent the chiral ligand scaffold,[17] when (*S*,*S*)-**7** and (*R*,*R*)-**7** are ionized to give the π-allylpalladium complexes **23** and **26**, respectively, it is clear that ionization to **23** is a matched case, whereas ionization to give **26** is mismatched due to steric interactions between the ionized substrate and ligand walls. This is consistent with the stereochemistry of the observed product **12**, which seems to arise from alkylation of **23**. When the two possible π-allylpalladium complexes formed by ionization of *meso*-**8** are examined, it seems that the matched ionization to form **24** leads towards the unobserved product **13**, while in contrast, mismatched ionization to form **25** leads to the observed product. When the four π-allylpalladium complexes are compared, it is reasonable to believe that **26** is of a higher energy than **24** and therefore **26** may not be attainable by direct ionization of (*R*,*R*)-**7** and also may be the less populated between **24** and **26**. It is also reasonable that **25** is of higher energy than **23** favoring conversion to **23** from **25**. Between the two sets of possibly interconvertible π-allylpalladium complexes, the two that arise from matched ionization events (**23** and **24**) are favored. What remains unclear is why **23** is preferentially alkylated over any of the other three complexes. It may be that **23** is the most stable complex and the most highly populated state, which leads to increased probability that it will be alkylated. This may have something to do with the pendant carboxylate. If the carboxylate ligates palladium in **23** the remaining vinyl group is forced to point away from the ligand assembly, while ligation of palladium in **24** orients the vinyl group toward the ligand. It is then possible that **24** is in fact alkylated, but by the pendent carboxylate, not an external nucleophile, leading back to *meso*-**8**. If the reaction between **24** and *meso*-**8** is rapid and reversible and (*R*,*R*)-**7** is not ionized to a great extent, then a situation that involves kinetic resolution of the *rac*-**7** and nonproductive matched ionization concurrent with a productive mismatched ionization of *meso*-**8** leading to **12** is likely.

This rationale assumes that ionization occurs to give the *syn* complexes, but another possibility is that ionization occurs directly to give the *anti* complexes. As summarized in Scheme 4, this scenario would allow for the matched ionization of **8** to lead to the observed product after two π–σ–π interconversions occurring sequentially at the primary then secondary carbon atoms. For the mechanism to produce the observed product, the stereogenic allylic alcohol with the *R* designation in the *meso* diol must be ionized and alkylated with inversion to give the *S* product, while the *S* stereocenter must be retained. At first glance it would appear to be unfavorable to ionize in the *anti* fashion due to steric interactions between the R group and the ligand assembly. However, the palladium-catalyzed asymmetric allylic alkylation of cyclic *meso* substrates works exceedingly well using diphenylphosphinobenzoic acid based ligands.[18] These reactions, by the cyclic nature of the substrates, "force" two groups into the *anti*,*anti* configuration. After ionization, **28** can then undergo π–σ–π interconversion to form **29** and place the R group in a flap region. Further π–σ–π interconversion, this time at the secondary carbon, would then form the *syn* complex **23** and after alkylation **12**.

It is important to note that alkylation of complexes **27**–**29** at the primary carbon would lead to a *Z* olefin, while alkylation of any of the intermediates in Scheme 3 would lead to *E* olefins. Since linear products are obtained with phenol nu-



Scheme 3. Proposed mechanism involving all-*syn* complexes.



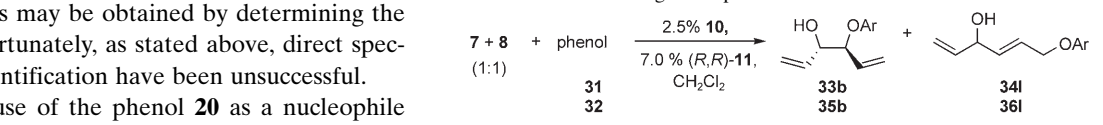
Scheme 4. Proposed mechanism involving *anti* complexes.

While the *ee* values of the branched products were greater than 99% in both cases, the most important observation, easily determined by ^{1}H NMR in this case, was that the linear product **36l** contained an *E* double bond derived from alkylation of a *syn*-complex. To date, all linear products obtained contain a single olefin isomer whose geometry had been obscured by overlapping ^{1}H NMR signals at up to 600 MHz. If the assumption is made that the linear products are of the same double bond geometry as **36l**, this can be interpreted as additional evidence in favor of the all-*syn* mechanism (Scheme 3).

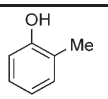
cleophiles, experimental evidence in favor of or eliminating one of the mechanisms may be obtained by determining the olefin geometry. Unfortunately, as stated above, direct spectroscopic means of identification have been unsuccessful.

In addition to the use of the phenol **20** as a nucleophile that functions as a protected alcohol in the product, it may be desirable to use phenols whose structures are retained in the final product. It was previously determined that the *ortho* methyl group in **20** is necessary to improve the regiochemistry of nucleophilic addition to an acceptable ratio. When other *ortho*-substituted aromatic alcohols such as *ortho*-cresol **31** and 1-naphthol **32** were employed in the reaction, the regiochemistry of the addition was eroded giving only 47:16 and 5:2 ratios, respectively (based on isolated yields, see Table 4). With the pure *R*,*R* ligand, the enantiopure monoarylated vicinal diols **33b** and **35b** were isolated in 47 and 50%, respectively.

Table 4. Pd AAA using other phenols.



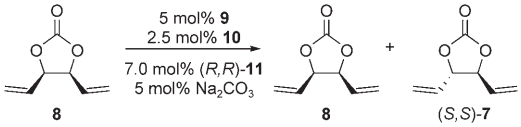
31
32
33b
35b
34l
36l

Entry	Phenol	Yield **b** [%]	Yield **l** [%]
1[a]		50	15
2[b]		47 (63)[c,d]	16
	31		
3[a]		63	26
4[b]		50 (67)[c,d]	20
	32		

[a] racemic ligand, RT, 1.1 equiv phenol. [b] (*R*,*R*)-**11**, 0°C, 0.8 equiv phenol. [c] >99% *ee*. [d] Based on 75% maximum yield.

Inspection of the two proposed mechanisms and the fact that both the *meso* and *dl* compounds give the same product may suggest that there may be an interconversion between the *dl* and *meso* isomers. Since the reaction forms (*S*,*S*)-**12** and leaves unreacted (*R*,*R*)-**7** when employing the (*R*,*R*)-naphthyl ligand, the product must be derived from both **8** and (*S*,*S*)-**7**. If it is assumed that the product is produced by the standard π-allylpalladium inversion–inversion mechanism,[8] (*S*,*S*)-**12** is derived directly from (*S*,*S*)-**7**. The question then arises as to whether the product can be produced directly from **8** or if the *meso* compound can be converted to (*S*,*S*)-**7** which is then converted to product. To determine the feasibility of converting **8** into one or both of the *dl* isomers of **7**, **8** was treated under the standard reaction conditions, but with only enough phthalimide to generate the active catalyst (Table 5). Under conditions employing

Table 5. Substrate interconversion.



Entry	*T* [°C]	Yield **8** [%]	Yield **7** [%]	*ee* (*S*,*S*)-**7** [%]
1[a]	25	trace	14	nd
2[b]	25	21	21	75
3[b]	−25	64	12	53

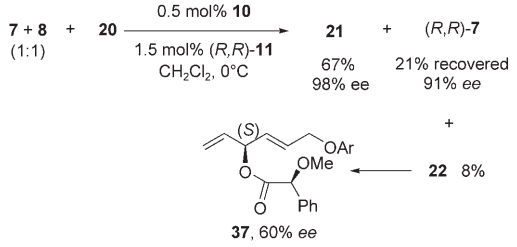
[a] N_2, 1 atm. [b] CO_2, 1 atm.

10 mol% phthalimide, 5 mol% π-allylpalladium chloride dimer, and 15 mol% (*R*,*R*)-naphthyl ligand at room temperature, (*S*,*S*)-**7** was recovered in 14% isolated yield, with **8** only observable in a trace amount by TLC (entry 1). In contrast, when the reaction is run under an atmosphere of CO_2, the mass recovery improves (entry 2). A 1:1 mixture of the *cis* and *trans* cyclic carbonates were recovered in 42% combined yield. By isolation and reduction of the *trans* compound to the diol, it was determined by chiral GC analysis and the sign of the optical rotation that the compound thus obtained was (*S*,*S*)-**7** in 75% *ee*. This result indicates that it is possible to convert **8** into the *dl*-cyclic carbonate **7** under the reaction conditions, and that the major enantiomer observed is that which leads to product. The still relatively low mass recovery is believed to be due to decomposition of the π-allylpalladium complexes in the absence of nucleophile, possibly through loss of CO_2.

Upon inspection of the two proposed mechanisms, it should be noted that in the *anti* mechanism (Scheme 4) matched ionization of **8** is believed to lead to product in contrast to the all-*syn* mechanism (Scheme 3) where a mismatched ionization is believed to give the product. It would be predicted that the *ee* observed upon conversion of **8** to (*S*,*S*)-**7** in the absence of an external nucleophile may be dependent on the reaction temperature. Under normal circumstances, the desired reaction is typically that of a matched substrate catalyst pair, which usually gives higher *ee* values at lower temperatures. This is the predicted result if the *anti* mechanism (Scheme 4) is operating. Reaction by the pathway illustrated in (Scheme 3), the all-*syn* mechanism, would be predicted to exhibit an inverse temperature dependence, that is, lower *ee* at lower temperature.

When **8** is allowed to react under conditions employing 10 mol% phthalimide, 5 mol% π-allylpalladium chloride dimer, and 15 mol% (*R*,*R*)-naphthyl ligand but at −25 °C, the *trans* isomer was isolated in 12% yield, with **8** recovered in 64% yield (Table 5, entry 3). Most importantly, the *ee* of isolated (*S*,*S*)-**7** had dropped significantly to 53%. The reduced enantiomeric excess, due to this 50 °C change in temperature is consistent with the all-*syn* mechanism.

To determine exact amounts of the starting materials and products present upon completion of the reaction, the reaction illustrated in Scheme 5 was tediously purified by repeated silica gel chromatography. Both the linear product **22** and the branched alcohol **21** were isolated in 8 and 67% yield, respectively, and 21% of the cyclic carbonate (*R*,*R*)-**7** was recovered.



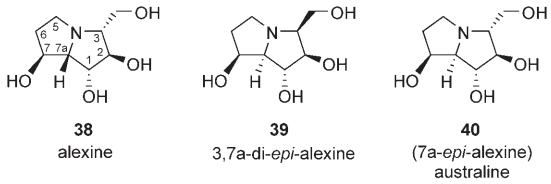
Scheme 5. Determination of the linear product's absolute configuration.

The *ee* values of **21** and **7** were determined by the normal methods to be 98 and 91%. On a variety of chiral stationary phase HPLC columns, the *ee* of **22** could not be determined so the *O*-methyl mandalate method was used to assign the absolute stereochemistry as *S* with 60% *ee*.[19] This result is also consistent with the all-*syn* mechanism. The unreacted starting material (*R*,*R*)-**7** is recovered in high yield (25% theoretical max), indicating a kinetic resolution of *rac*-**7**. The remaining 75% of the starting cyclic carbonates are nicely incorporated into the alkylation products **21** and **22**, which derive from π-allylpalladium complexes **23** and **25**. All experimental evidence collected to date points towards the all-*syn* mechanism illustrated in Scheme 3.

The principle difference between the phenol and phthalimide reactions is the solubility of the nucleophile. Phthalimide is only partially soluble, while the phenols completely dissolve under the reaction conditions. With phthalimide, a proper balance between the relative rates of ionization, equilibration, and nucleophilic addition is presumably achieved, but the higher concentration of phenol present in the reaction mixture must increase the rate of nucleophilic addition relative to equilibration of the π-complexes and lead to a less regioselective reaction.

Total synthesis of (+)-australine hydrochloride: We have previously reported the use of monoprotected diol **21** as a convenient building block.[16] To demonstrate the utility of the phthalimide derived product, we sought to employ the N-protected aminoalcohol **12** in a synthesis of an alkaloid. Since **12** contains the heteroatoms in a 1,2-*syn* arrangement with the remaining carbons in an oxidation state suitable for further functionalization, alkaloid glycosidase inhibitors seemed to be a logical target. More specifically, the potential use of **12** in the preparation of the polyhydroxylated pyrrolizidine alkaloid australine **40** was investigated.

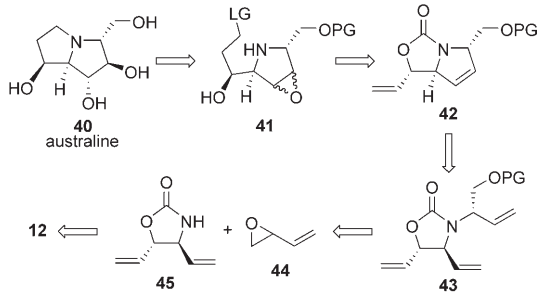
Australine[20] is a particularly interesting target for a multitude of reasons, not the least of which is its highly oxygenated bicyclic core structure containing five contiguous stereogenic centers. In addition, several structurally related alkaloids mainly differing in the stereochemical orientation of the substituents appended to the core have been isolated.[21] While alexine (**38**) was the first of this family to be isolated, other epimeric natural products such as **39** and **40** soon followed. These compounds are potent and specific glycosidase



inhibitors. For example, australine was isolated from the rainforest tree *Castanospermum australe*[20] and is a μM inhibitor of α-glucosidase amyloglucosidase.[22] These compounds and synthetic analogues thereof are attractive drug targets in the therapeutic areas of cancer, diabetes, and obesity and may potentially be used as antiviral agents. While several syntheses of australine **40** and its corresponding hydrochloride salt have been reported,[23] it was hoped that application of compounds derived from **12** in further palladium-catalyzed reactions may lead to a general synthetic strategy to access multiple diastereomeric natural products.

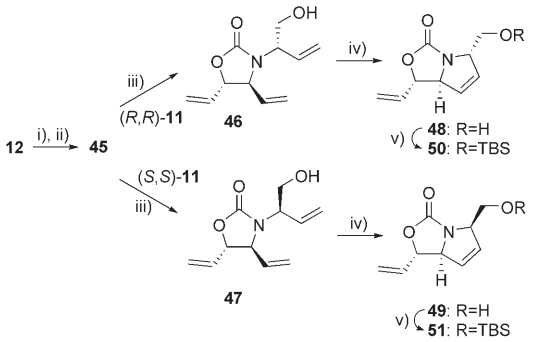
Our retrosynthetic strategy is outlined in Scheme 6 and relies on a late stage epoxide ring opening to set the all-*trans* orientation of the substituents. Based on our previous work on similar systems, we believed that ring opening of both of the diastereomeric intermediates corresponding to **41** should yield a single diastereomer.[24] This intermediate would then be cyclized to form australine. Pyrrolidines **41** should be accessible from the oxazolidinone **42** by functionalization of the monosubstituted olefin and epoxidation of the remaining 3-pyrroline. It was believed that **42** should be readily available from **43** by a chemoselective ring-closing metathesis reaction, and that **43** should be accessible by the palladium-catalyzed DYKAT reaction of **44** with nitrogen nucleophile **45**. The oxazolidinone **45** should be easily prepared from **12**.

Initial studies sought to answer questions about the feasibility of the palladium-catalyzed ring opening of **44** with **45**.



Scheme 6. Retrosynthetic analysis of australine.

Previous studies from our group have demonstrated that oxazolidines are good substrates for these reactions,[24] but 4,5-disubstituted-oxazolidinones hadn't been explored. The key issues involved the diastereoselectivity of the reaction. It needed to be determined if the reaction would be catalyst or substrate controlled, if **43** can be formed selectively, and how well will the ring-closing metathesis (RCM) reaction of **43** would perform. To answer these questions, the conditions previously established were employed using both enantiomers of the naphthyl ligand (Scheme 7).

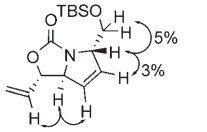


Scheme 7. Diastereoselective alkylation of butadiene monoepoxide. i) $H_2N(CH_2)_2NH_2$, EtOH, 96%; ii) triphosgene, pyr., CH_2Cl_2, 78%; iii) 0.5 mol% $[Pd_2dba_3]\cdot CHCl_3$, 1.5 mol% **11**, 10 mol% DBU, CH_2Cl_2, (*R*,*R*)-**11**: 95:5 dr **46**/**47**, 99%, (*S*,*S*)-**11**: 4:96 dr **46**/**47**, 98%; iv) 1 mol% Grubbs 2nd-generation catalyst, CH_2Cl_2, **48**: 77%, **49**: 73%; v) TBSCl, imidazole, CH_2Cl_2, **50**:91%, **51**:99%.

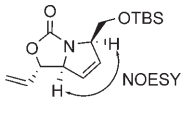
The requisite oxazolidinone **45** was easily prepared in two steps from **12** in high yield. Under optimized conditions, when **45** was allowed to react with **44** in the presence of 0.5 mol% $[Pd_2dba_3]\cdot CHCl_3$, 1.5 mol% ligand, and 10 mol% DBU in CH_2Cl_2, a mixture of ring-opened products **46** and **47** was formed. After subsequent transformation, it was determined that employing the *R*,*R*-naphthyl ligand, diastereomer **46** was preferentially formed along with **47** as an inseparable mixture in a 95:5 ratio as determined by GC while the *S*,*S*-naphthyl ligand gave a 4:96 ratio favoring **47**. As determined in initial experiments with higher catalyst loadings (2.0 mol% $[Pd_2dba_3]\cdot CHCl_3$, 6.0 mol% ligand), the *S*,*S*-naphthyl ligand and (*S*,*S*)-**45** seem to be the matched pair. This reaction gives a higher diastereomeric ratio and yield (95 vs 83%) in a shorter reaction time (2.5 vs 5.5 h as

judged by a characteristic color change from the yellow reaction color to an orange resting catalyst color).

Preliminary experiments focused on first protecting the alcohols **46** and **47** as their TBS ethers followed by ring-closing metathesis using Grubbs first-generation catalyst[25] to provide **50** and **51**, at which stage their relative configura-



50

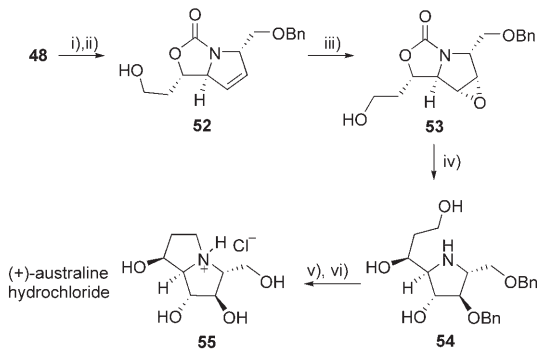


51

tions (and therefore those of **46** and **47**) were determined by NOE DIFF and NOESY experiments. It was later found, as illustrated in Scheme 7, that using the unprotected alcohols **46** and **47** directly, RCM could be effected in good yield employing Grubbs second-generation catalyst. Protection of the resultant primary alcohols gave the TBS ethers in high yield. It was also fortuitous that **48** and **49** were separable by careful chromatographic purification, whereas none of the other sets of diastereomers could be cleanly separated.

With one of the two pyrrolizidine rings now formed and three of the stereogenic centers established, the two main objectives were to introduce the remaining oxygenated stereocenters and to transform the remaining terminal olefin into a group suitable for the formation of the fused ring. It was decided to first try to take advantage of the free hydroxyl group in **48** and to do a directed epoxidation of the proximal disubstituted olefin. While it is postulated that the diastereoselectivity of the reaction is irrelevant, the formation of a single diastereomer is preferable for characterization purposes and for further transformations. The chemoselectivity of the reaction was of some concern as both the desired olefin and the monosubstituted olefin were both electron deficient and predicted to react sluggishly. At prolonged reaction times, using *m*CPBA buffered with $NaHCO_3$ in CH_2Cl_2, no reaction is observed. Using the more reactive trifluoroperacetic acid, a myriad of products was observed. The use of methyltrioxorhenium (MTO) with urea hydrogen peroxide adduct as the terminal oxidant did provide the epoxide in good yield as one diastereomer, but was difficult to reproduce.

Since epoxidation of **48** was problematic, it was decided that it would likely be easier to change the order of the transformations, that is, to first install a group suitable for forming the second ring. The monosubstituted olefin of **48** would be predicted to be selectively hydroborated in the presence of the disubstituted olefin and the resulting alcohol could be transformed into a variety of leaving groups. To this end, the free alcohol of **48** was first protected as a benzyl ether in 94% yield using the benzyl 2,2,2-trichloroimidate method.[26] Hydroboration followed by sodium perborate oxidation[27] then smoothly provided the primary alcohol **52** (Scheme 8). The remaining olefin was epoxidized



Scheme 8. Completion of the synthesis. i) Benzyl 2,2,2-trichloroacetimidate, TfOH, 94%, ii) 9-BBN, THF; $NaBO_3 \cdot H_2O$, H_2O, 74%; iii) Oxone, trifluoroacetone, $NaHCO_3$, MeCN/aqueous EDTA, 0°C, 67%; iv) Dowex 1X8-50, BnOH, 100°C, 51%; v) MsCl, Et_3N, CH_2Cl_2, 74%; vi) H_2, $PdCl_2$, MeOH, 98%.

with in situ generated methyl trifluoromethyl dioxirane[24] to give **53** as a single diastereomer in 67% yield.

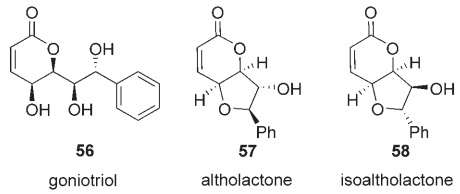
To finish the synthesis, it was necessary to remove the oxazolidinone carbonyl group, open the epoxide, and cyclize to form the pyrrolizidine. Solvolysis of the oxazolidinone was first attempted by using resin bound base.[28] Under the reported conditions (Dowex 1X8-50, HO^- form in methanol at room temperature) no reaction occurred. The heterogeneous mixture was heated to 65°C overnight where partial conversion to a single additional compound was observed by ^1H NMR spectroscopy.

After considerable experimentation, it was determined that both the oxazolidinone and epoxide moieties of **53** had been solvolyzed under the reaction conditions, forming a single adduct that had incorporated a molecule of methanol. It would be beneficial to do both the hydrolysis and epoxide ring opening in a single step; however, incorporation of a methoxy group would certainly need to be avoided. While there are no reports of the same conditions using alcohols other than methanol, the obvious choice was to employ benzyl alcohol because, in addition to solvolyzing the oxazolidinone and opening the epoxide, it would also serve as a protecting group. Under similar conditions, using benzyl alcohol at 100°C for 9 h, the desired reaction was effected, forming **54** in 67% yield as a single diastereomer assigned the all-*trans* stereochemistry illustrated in Scheme 8. Based on analogy to our previous experience opening 3-pyrroline oxides,[24] this assumption seemed reasonable and conversion to the natural product after two additional steps would later confirm the stereochemistry.

With a good source of **54** in hand, the final stages required cyclization of the free amine with loss of the primary alcohol to form the pyrrolizidine and deprotection of the two benzyl groups to form australine. Cyclization was promoted by selective formation of the primary mesylate by using standard conditions at −30°C with concomitant displacement by the secondary amine to form the pyrrolizidine in 74% yield (Scheme 8). It was decided to remove the benzyl groups using $PdCl_2/H_2$[25] because it would give the

HCl salt directly. This was desirable because literature reports indicated that free australine was not nearly as stable as its hydrochloride salt.[23f] In the event, (+)-australine hydrochloride was formed in 98% yield whose ^{1}H, ^{13}C and IR spectra as well as optical rotation matched the literature data.[23f]

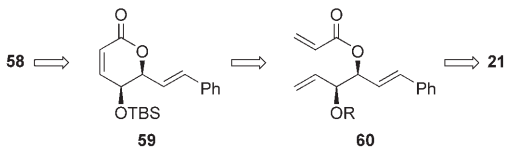
Formal synthesis of isoaltholactone by chemoselective metathesis reactions: In addition to the use of the phthalimide derived product, we were also interested in exploring chemoselective reactions of the monoprotected diene diol in the context of a synthesis. We were first attracted to the natural product goniotriol **56** because of the readily apparent *syn* diol motif flanked by an alkene and an additional diol that could potentially be derived from oxidation of an olefin. Goniotriol is part of a family of so-called styryl lactones and shares structural similarity to many natural products including altholactone **57** and isoaltholactone **58**.[29] This family of natural products has a diverse biological activity, with altholactone **58** being one of the most cytotoxic com-



pounds in general while isoaltholactone is selective for HT-29 colon cancer cells.[30] There has been significant interest in these compounds due to their cytotoxicity and many total syntheses have appeared largely relying on the chiral pool for starting materials.[31] The development of a synthetic strategy that relies on a catalytic enantioselective method to set the initial stereochemistry would provide a facile entry to this class of compounds, and we set our sights on isoaltholactone.

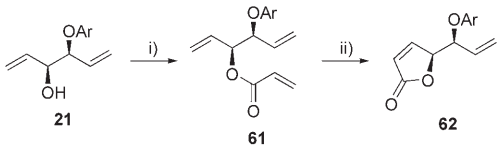
Our initial retrosynthetic analysis relied upon the known conversion of the protected styrene **59** to isoaltholactone **58** by chemoselective epoxidation of the styryl olefin with concomitant TBS deprotection and cyclization of the resulting free alcohol to form the natural product (Scheme 9).[32] It was believed that the α,β-unsaturated lactone could be formed by RCM of a suitable protected acrylic ester **60**, and that the necessary compound would be readily available by a chemoselective phenylation of the monoprotected diol **21**.

At the outset of this work, it was unclear whether RCM of a triene such as **61** would form the desired six-membered



Scheme 9. Retrosynthetic analysis of isoaltholactone.

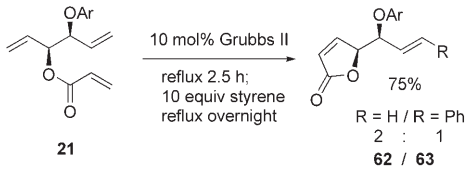
ring or the five-membered butenolide. To probe this issue, an acryloyl group was easily introduced in good yield to form **61** (Scheme 10), and RCM experiments followed. Attempts to use the standard Grubbs first-generation catalyst



Scheme 10. Initial selectivity experiments. i) Acryloyl chloride, DMAP, Et_3N, CH_2Cl_2, 0°C→RT, 71%; ii) 10 mol% Grubbs 2nd-generation catalyst, CH_2Cl_2, reflux 2.5 h, 70%.

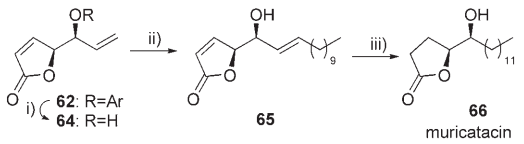
failed even at prolonged reaction times, while the second-generation catalyst provided the butenolide **62** in 2.5 h. The five-membered lactone was formed completely selectively over the six-membered ring. During the course of our initial investigation, similar observations were reported.[33]

Since the butenolide was so easily formed, it was decided to move forward and try to introduce the phenyl group and later expand the ring. The desired ring system would hopefully be obtained once the alcohol is deprotected and exposed to equilibrating conditions to "walk" the ester one alcohol over and form the desired six-membered ring. The triene **21** was exposed to the previous conditions that provided the butenolide followed by introduction of styrene and prolonged reaction time to hopefully do cross-metathesis (CM) on the remaining monosubstituted olefin. Surprisingly, **62**, which is the product of only RCM, resulted as the major product along with the desired styrene **63** in a combined yield of 75% (Scheme 11).



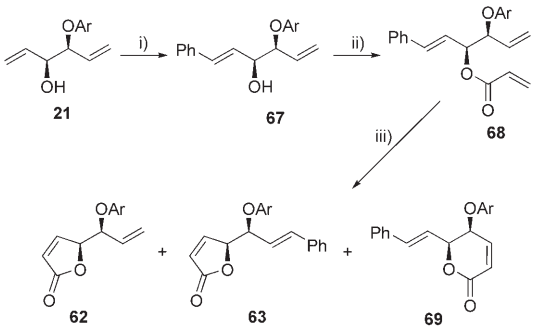
Scheme 11. Attempted tandem RCM/CM.

This result was fairly unexpected as a relatively high catalyst loading and styrene concentration as well as a long reaction time afforded only a small percentage of the product incorporating a phenyl group. Additionally, it is in contrast to a previous report where the alcohol is protected as a TBS ether and the tandem RCM/CM process works well.[23b] It was postulated that the electron-rich aryl ether was somehow responsible for the lack of reactivity of the monosubstituted olefin.[34] To test this, the ether was oxidatively cleaved using CAN in aqueous acetonitrile to provide **64** in 70% yield (Scheme 12). CM with dodecene under our standard conditions did indeed smoothly provide **65** which also led to a synthesis of muricatacin **66** after hydrogenation.[35]



Scheme 12. Synthesis of muricatacin. i) CAN, CH_3CN/H_2O, 70%; ii) 5 equiv dodecene, 10 mol% Grubbs 2nd-generation catalyst, CH_2Cl_2, reflux 1 h, 84%; iii) H_2, Pd/C, 93%.

Since such difficultly was being encountered in attempts to introduce the phenyl group on the allylic aryl ether, it was postulated that the aryl moiety was somehow slowing the reaction at this position and that a chemoselective cross-metathesis reaction may be possible with the acyclic precursor **21**. Under our standard initial conditions, the styryl group was then selectively introduced in 72% yield to the free alcohol allylic double bond as one geometrical isomer (Scheme 13). To form the desired synthetic intermediate **62**,

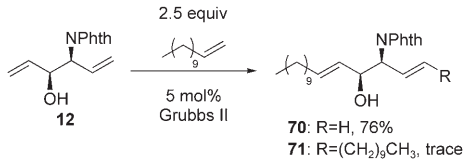


Scheme 13. Attempted RCM. i) 10 mol% Grubbs 2nd-generation catalyst, 10 equiv styrene, CH_2Cl_2, reflux 2.5 h, 72%; ii) acryloyl chloride, DIPEA, CH_2Cl_2, 0°C, 88%; iii) 10 mol% Grubbs 2nd-generation catalyst, CH_2Cl_2, reflux 16 h, then 10 additional mol% cat. reflux 24 h, **69**: 27%, mixture of **62** and **63**: 30%.

the free alcohol was acylated to append the acryloyl group and RCM attempted. At this point, it was thought that the RCM reaction of **68** should smoothly produce the desired product because the reaction is between two monosubstituted olefins. Unfortunately, in the event, what was observed under forcing conditions was a mixture of three compounds including the desired product **69** in 27% and the two previously prepared butenolides **62** and **63** in a combined yield of 30%.

Since in the attempted RCM of **68**, the disubstituted olefin competes with the monosubstituted aryl ether olefin, cross-metathesis between styrene and **21** selectively reacts with the non-aryl allylic alkene to provide **67**, and cross-metathesis of **62** effectively fails, the difficulty must be due to the aryl moiety. This fact should prove useful when it is necessary to protect an allylic alcohol from ruthenium-catalyzed metathesis reactions. In the present case it would then follow that deprotection of the aryl group should eliminate the current problems. Unfortunately all attempts to oxidatively deprotect **67** to the free alcohol were unsuccessful. It is noteworthy that the only time it has proven difficult to remove this group to date is on compounds that have a styryl double bond.

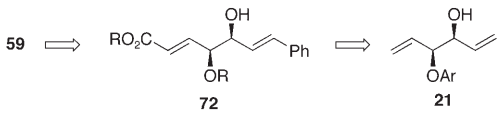
Since the CM and RCM of **21** are both highly chemoselective reactions, cross-metathesis of phthalimide **12** with dodecene was attempted to determine if this is a general trend of this type of diene. Under the conditions illustrated in Scheme 14, the desired product **70** was obtained along with



Scheme 14. CM of *N*-protected amino diene.

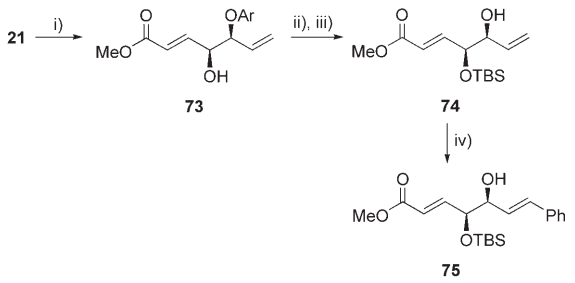
a trace of the doubly reacted product **71**. When five equivalents of olefin and 10 mol% Grubbs second-generation catalyst was used, our standard initial conditions, **70** was isolated in 62% yield along with 12% of **71**. So clearly the second olefin of **12** is much more reactive towards metathesis than **21**, further evidence that the electron-rich arene plays a major role in deactivating the olefin.

Since the absolute configuration of **21** is *S*,*S*, it does not matter which olefin the phenyl group is appended to and consequently which olefin is used to form the lactone. As long as the sequence is chemoselective for one of the olefins, and the molecule is suitably protected, the penultimate intermediate **59** should be accessible. With this in mind, and due to difficulty encountered in attempts to cleanly remove the aryl ether, it was then postulated that **59** should be accessible by isomerization of the *trans*-α,β-unsaturated double bond of an intermediate such as **72** (Scheme 15) to *cis* followed by lactone formation. This compound could hopefully be prepared by two selective cross-metathesis reactions on **21** with the introduction and removal of the aryl group to allow for protecting groups to be introduced in the proper order.



Scheme 15. Revised retrosynthetic analysis.

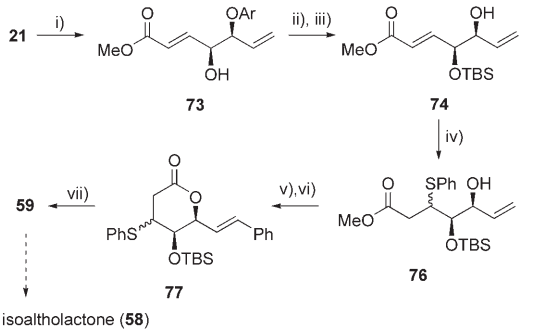
Initial studies were focused on selectively functionalizing the termini via chemoselective cross-metathesis reactions. Although the CM between a secondary allylic alcohol and an acrylate may not be predicted to be a good reaction,[36] the acrylate **73** was isolated in 60% yield as the *E* olefin with no reaction observed on the allylic ether olefin. The free alcohol was then protected as its TBS ether and the aryl ether oxidatively cleaved using ceric ammonium nitrate to give **74** in 68% over two steps (Scheme 16). Cross-metathesis of **74** with styrene using Grubbs second-generation



Scheme 16. Sequential functionalization of the termini. i) 5 equiv methyl acrylate, 10 mol% Grubbs 2nd-generation catalyst, CH_2Cl_2, reflux 1 h, 60%; ii) TBS-OTf, 2,6-lutidine, CH_2Cl_2; iii) CAN, CH_3CN/H_2O, 68% (2 steps); iv) 5 equiv styrene, 10 mol% Grubbs 2nd-generation catalyst, CH_2Cl_2, reflux 16 h, 59%.

catalyst then provided **75** in 59% yield, demonstrating that the initial chain in **21** can be extended in both directions with the introduction of functional groups that allow for further differentiation.

While this sequence demonstrates that it is possible to introduce the functional groups necessary for isoaltholactone, further optimization was necessary to reduce the amount of catalyst used and to provide enough material to complete the synthesis. To this end, **73** was obtained in 69% yield using 2 mol% Grubbs second-generation catalyst with five equivalents of methyl acrylate by refluxing for 2 h in CH_2Cl_2. The TBS group was then introduced using TBSCl in 98% yield, and the aryl ether was deprotected using CAN in acetonitrile and water to provide **74** in quantitative yield. At this point the second CM was postponed until after lactonization to avoid any potential for metathesis on the undesired olefin. The lactone was then formed in a two step process involving conjugate addition of benzenethiol and cyclization. Initially, **74** was treated with benzenethiol and piperidine in acetonitrile at 85°C according to the procedure of Tanikaga.[37] Finally, we attempted the conjugate addition of benzenethiol by simply stirring **74** (Scheme 17) in benzenethiol as the solvent with a catalytic amount of triethylamine. After 16 h, the starting material had disappeared and four new spots, which correspond to the two diastereomers of the acyclic methyl ester **76** and the two diastereomers of the lactone appeared in 83% combined yield. All four products can be separated by column chromatography but were routinely subjected to the next step as the mixture.



Scheme 17. Formal synthesis of isoaltholactone under optimized conditions. i) 5 equiv methyl acrylate, 2 mol% Grubbs 2nd-generation catalyst, CH_2Cl_2, reflux 2 h, 69%; ii) TBSCl, imidazole, CH_2Cl_2, 98%; iii) CAN, CH_3CN/H_2O, quantitative; iv) PhSH, Et_3N, 83%; v) Otera's cat. toluene, 85% (77% over two steps if products not separated); vi) 5 equiv styrene, 5 mol% Grubbs 2nd-generation catalyst, CH_2Cl_2, reflux 16 h, 90%; vii) DBU, CH_2Cl_2, 89%.

In order to lactonize the acyclic methyl ester to form the precursor to **77**, the products were taken up in toluene and heated at reflux for 4 h. This, however, did not lead to disappearance of the methyl ester or additional formation of lactone. Otera's tin catalyst[38] was added and after 2 h at reflux in toluene all acyclic methyl ester **76** had lactonized in 85%. Without separation of products, running this two-step sequence in succession resulted in a combined yield of 77%. The next step involved another cross-metathesis to introduce the styryl functionality. Treating **14** with styrene and Grubbs second-generation catalyst in refluxing methylene chloride overnight gave compound **77** in 90% yield. Elimination of benzenethiol with DBU in CH_2Cl_2 also proceeded uneventfully, to complete the formal synthesis providing **59** in 89% yield.

Conclusion

In summary, we have developed a simple, three-step, catalytic enantioselective procedure to produce synthetically useful monoprotected diols and N-protected aminoalcohols in high *ee* from a mixture of *dl*- and *meso*-1,2-divinylethylene carbonate that is easily prepared from the commodity chemical acrolein. Although the process did not proceed as was initially expected, an interesting mechanism involving both a kinetic resolution and desymmetrization in a convergent process is proposed. The present study demonstrates how well a series of equilibrating intermediates can behave when a proper balance of the relative variables is achieved and may potentially lead to further examples where mismatched substrate catalyst pairs also enter the reaction. Additionally, the compounds produced have been demonstrated to be useful synthons. Since each backbone atom in the product is differentiated, further chemoselective transformations should make a wide range of chiral compounds easily accessible for future syntheses. (+)-australine hydrochloride and isoaltholactone were easily prepared in a straightforward manner using this methodology. These syntheses nicely demonstrate further use of the products and feature a highly diastereoselective Pd-catalyzed ring opening of butadiene monoepoxide as well as a series of chemoselective ring-closing and cross-metathesis reactions.

Experimental Section[39]

***cis*- and *trans*-1,2-Divinylethylene carbonate (7** and **8)**: According to the procedure of Hekmatshoar,[7] acrolein (10.0 mL, 150 mmol) was added to a biphasic mixture of saturated aqueous ammonium chloride (225 mL)

and THF (375 mL). Zinc powder (1.95 g, 29.9 mmol) was then added in 1 portion and the biphasic mixture was allowed to stir overnight, at which point TLC analysis indicated that the starting material had been consumed. The crude reaction mixture was filtered over celite with CH_2Cl_2, diluted with water, and extracted with CH_2Cl_2. The combined organic extract was dried over magnesium sulfate and the solvent removed in vacuo. Two batches run at this scale were combined and flash chromatography (gradient, 20 to 30% EtOAc/petroleum ether) afforded a colorless oil (13.7 g, 80%) that was taken directly on.

According to the procedure of Braun,[5a] the diol (13.7 g, 120 mmol) was dissolved in diethyl carbonate (18.2 mL, 1.25 equiv) and potassium carbonate (0.0498 g, 0.361 mmol) was added. The flask was equipped with a shortpath distillation head, and the reaction mixture was heated to 115°C and maintained for 2 h, during which time ethanol distilled off. The crude product was cooled to RT and directly purified by flash chromatography (gradient, 10 to 30% EtOAc/petroleum ether) to afford the title compound as a pale yellow oil (14.4 g, 84%).

Pure samples of each compound were obtained by flash chromatography (gradient, 1 to 20% EtOAc/petroleum ether):

***trans*-1,2-Divinylethylene carbonate (7)**: $R_f = 0.40$ (20% EtOAc/petroleum ether); ^{1}H (300 MHz, $CDCl_3$): δ = 5.93–5.82 (m, 2H), 5.48 (d, J = 16.8 Hz, 2H), 5.43 (d, J = 10.2 Hz, 2H), 4.76–4.65 ppm (m 2H); ^{13}C NMR (75 MHz, CDCl3): δ = 153.9, 131.0, 121.7, 82.4 ppm; IR (neat): $\tilde{\nu}$ = 3095, 2996, 2929, 1806 cm^{-1}; HRMS (EI): m/z: calcd for $C_6H_7O_3$: 95.0497, found 95.0496 [$M-CO_2H^+$].

***cis*-1,2-Divinylethylene carbonate (8)**: $R_f = 0.32$ (20% EtOAc/petroleum ether); ^{1}H (300 MHz, $CDCl_3$): δ = 5.81–5.70 (m, 2H), 5.47 (d, J = 17.7 Hz, 2H), 5.42 (d, J = 11.1 Hz, 2H), 5.19–5.13 ppm (m 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.2, 129.8, 121.4, 80.0 ppm; IR (neat): $\tilde{\nu}$ = 3094, 2995, 1805 cm^{-1}; HRMS (EI): m/z: calcd for $C_6H_7O_3$: 95.0497, found 95.0489 [$M-CO_2H^+$].

(3*S*,4*S*)-4-*N*-Phthalimido-1,5-hexadiene-3-ol (12): Sodium carbonate (0.0265 g, 0.25 mmol), phthalimide **9** (0.8092 g, 5.5 mmol), (*R*,*R*)-**11** (0.1186 g, 0.15 mmol), and π-allylpalladium chloride dimer (0.0183 g, 0.05 mmol) were tared into a 100 mL flask. The reaction vessel was evacuated for a period of 5 min, then backfilled with nitrogen. The procedure was repeated two additional times before CH_2Cl_2 (30.0 mL, degassed by freeze/pump/thaw method) was added, and the resulting suspension allowed to stir for 15 min. A 1:1 mixture of the cyclic carbonates **7** and **8** (0.7006 g, 5.0 mmol) was tared into a small flask, purged with argon for 15 min, dissolved with CH_2Cl_2 (10.0 mL, degassed by freeze/pump/thaw method), and added to the reaction mixture. After stirring for 72 h at room temperature, the solvent was removed in vacuo and the reaction mixture was directly applied to a column and subjected to flash chromatography on silica gel (gradient, 5 to 25% EtOAc/petroleum ether) to afford **15** (0.9015 g, 74%). $R_f = 0.20$ (20% EtOAc/petroleum ether); $[\alpha]_D^{23}$ = −86.37 (c = 1.0, CH_2Cl_2); ^{1}H (300 MHz, $CDCl_3$): δ = 7.87–7.81 (m, 2H), 7.76–7.71 (m, 2H), 6.22 (ddd, J = 17.3, 10.4, 6.9 Hz, 1H), 5.83 (ddd, J = 15.3, 10.5, 4.7 Hz, 1H), 5.43–5.15 (m, 4H), 4.89 (app t, J = 6.6 Hz, 1H), 4.72–4.65 (m, 1H), 3.52 ppm (d, J = 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8, 137.3, 134.2, 132.1, 131.6, 123.5, 118.8, 116.8, 72.7, 58.6 ppm; IR (neat): $\tilde{\nu}$ = 3463, 1707, 1387 cm^{-1}; HRMS (EI): m/z: calcd for $C_{11}H_6NO_3$: 186.0555, found 186.0545 [$M-C_3H_5O^+$].

Large-scale preparation of 12: Sodium carbonate (0.1060 g, 1.0 mmol), phthalimide (2.2364 g, 15.2 mmol, 0.76 equiv), (*R*,*R*)-naphthyl ligand (0.2373 g, 0.30 mmol, 1.5 mol%), and π-allylpalladium chloride dimer (0.0366 g, 0.10 mmol, 0.5 mol%) were tared into a 250 mL flask. The reaction vessel was evacuated for a period of 5 min, then backfilled with nitrogen. The procedure was repeated two additional times before CH_2Cl_2 (120.0 mL, degassed by freeze/pump/thaw method) was added, and the resulting suspension allowed to stir for 15 min. The cyclic carbonates **7** and **8** (2.803 g of a 1:1 mixture, 20.0 mmol) were tared into a flask, purged with argon for 15 min, dissolved with CH_2Cl_2 (40.0 mL, degassed by freeze/pump/thaw method), and added to the reaction mixture. After stirring for 96 h at room temperature, the solvent was removed in vacuo and the reaction mixture was directly applied to a column and subjected to flash chromatography on silica gel (gradient, 10 to 30% EtOAc/petroleum ether) to afford **12** (3.4200 g, 70%, 94% based on a maximum 75% conversion).

(*S*,*S*)-4-(4-Methoxy-2,3-dimethylphenoxy)hexa-1,5-dien-3-ol (21) and 6-(4-methoxy-2,3-dimethylphenoxy)hexa-1,4-dien-3-ol (22): 4-Methoxy-2,3-dimethylphenol (**20**; 0.5458 g, 3.6 mmol), (*R*,*R*)-**11** (0.0851 g, 0.11 mmol), and π-allylpalladium chloride dimer (0.0131 g, 0.036 mmol) were tared into a 100 mL Schlenk flask. The reaction vessel was evacuated for a period of 5 min, then backfilled with nitrogen. The procedure was repeated two additional times before CH_2Cl_2 (35 mL, degassed by freeze/pump/thaw method) was added, and the resulting suspension allowed to stir for 15 min before being cooled to 0°C in an ice bath. The cyclic carbonates **7** and **8** (0.6527 g of a 1:1 mixture, 4.66 mmol) were tared into a vial, purged with nitrogen for 15 min, dissolved with CH_2Cl_2 (11.6 mL, degassed by freeze/pump/thaw method), and slowly added to the reaction mixture. The mixture was allowed to stir and slowly warm to 4°C at ambient rate over 48 h before being poured into a separatory funnel containing ether and 1 M NaOH. The layers were then separated and the organic layer washed with two additional portions 1 M NaOH and one brine. The ethereal solution was then dried ($MgSO_4$) and the solvent removed in vacuo. Flash chromatography (gradient 2 to 25% EtOAc/petroleum ether) afforded **21** as a pale yellow oil (0.6580 g, 59%) and **22** as a colorless oil (0.0569, 5%).

Data for 21: $R_f = 0.56$ (20% EtOAc/petroleum ether); $[\alpha]_D^{22}$ = +1.44 (c = 1.06, CH_2Cl_2); ^{1}H (300 MHz, $CDCl_3$): δ = 6.65 (AB_q, J = 9.0 Hz, $\Delta\nu_{AB}$ = 21.6 Hz, 2H), 5.97 (ddd, J = 16.5, 10.5, 5.4 Hz, 1H), 5.84 (ddd, J = 17.1, 10.8, 6.6 Hz, 1H), 5.47–5.25 (m, 4H), 4.43 (t, J = 6.6 Hz, 1H), 4.32 (br s, 1H), 3.77 (s, 3H), 2.63 (d, J = 3.6 Hz, 1H), 2.20 (s, 3H), 2.16 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.4, 149.5, 136.0, 134.4, 127.7, 126.6, 119.6, 117.4, 112.0, 107.7, 83.6, 74.8, 55.9, 12.6, 12.1 ppm; IR (neat): $\tilde{\nu}$ = 3453 cm^{-1}: HRMS (EI): m/z: calcd for $C_{15}H_{20}O_3$: 248.1412, found 248.1401 [M^+].

Data for 22: $R_f = 0.30$ (20% EtOAc/petroleum ether); $[\alpha]_D^{22}$ = −0.34 (c = 1.0, CH_2Cl_2); ^{1}H (300 MHz, $CDCl_3$): δ = 6.64 (AB_q, J = 9.3 Hz, $\Delta\nu_{AB}$ = 4.9 Hz, 2H), 6.00–5.87 (m, 3H), 5.30 (dt, J = 15.9, 1.2 Hz, 1H), 5.81 (dt, J = 10.2, 1.5 Hz, 1H), 4.71 (t, J = 4.8 Hz, 1H), 4.48 (d, J = 4.2 Hz, 2H), 3.78 (s, 3H), 2.19 (s, 3H), 2.17 (s, 3H), 1.79 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.1, 150.8, 139.1, 133.4, 127.3, 127.2, 126.7, 115.5, 109.7, 107.8, 73.2, 68.4, 56.0, 12.3, 12.1 ppm; IR (neat): $\tilde{\nu}$ = 3374, 1482, 1254, 1112 cm^{-1}. HRMS (EI): m/z: calcd for $C_{15}H_{20}O_3$: 248.1412, found 248.1405 [M^+].

(4*S*,5*S*)-3-((*S*)-1-Hydroxybut-3-en-2-yl)-4,5-divinyloxazolidin-2-one (46): (*R*,*R*)-**11** (0.0871 g, 0.11 mmol) and tris(dibenzylideneacetone)-dipalladium(0) chloroform adduct (0.0380 g, 0.037 mmol) were tared into a 100 mL flask. The reaction vessel was evacuated for a period of 5 min, then backfilled with nitrogen. The procedure was repeated two additional times before CH_2Cl_2 (54 mL, degassed by freeze/pump/thaw method) was added, followed by a solution of oxazolidionone **45** (1.0222 g, 7.35 mmol) in CH_2Cl_2 (20 mL), and the resulting solution was allowed to stir for 5 min before the DBU (0.1118 g, 0.73 mmol) was added. After five additional min, butadiene monoepoxide (0.5149 g, 7.3 mmol) was added and the mixture was allowed to stir at ambient temperature for 16 h before the solvent was removed in vacuo. Flash chromatography (gradient, 25 to 50% EtOAc/petroleum ether) afforded a mixture of diasteromers as a yellow oil(1.5371 g, quantitative yield).

Data for 46: $R_f = 0.39$ (50% EtOAc/petroleum ether); ^{1}H (500 MHz, $CDCl_3$): δ = 5.91–5.80 (m, 2H), 5.71 (ddd, J = 9.0, 10.0, 17.0 Hz, 1H), 5.43–5.14 (m, 6H), 4.56 (dd, J = 7.5, 6.5 Hz, 1H), 4.00–3.80 (m, 4H), 3.57 ppm (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.8, 134.1, 132.6, 132.1, 122.3, 121.4, 119.8, 119.6, 119.0, 80.3, 65.6, 62.9, 59.4 ppm; HRMS (EI): m/z: calcd for $C_{11}H_{13}NO_2$: 191.0946, found 191.0946 [$M-H_2O^+$].

(2*R*,3*R*,4*R*,5*R*)-4-(Benzyloxy)-5-(benzyloxymethyl)-2-((*S*)-1,3-dihydroxypropyl)pyrrolidin-3-ol (54):[40] Dowex 1X8 (Cl^- form) was activated in the following manner: The resin (approximately 1 g) was loaded into a Pasteur pipet and washed with 3 M NaOH (20 mL) then water (10 mL). The resin was then flushed with N_2 for 15 min to remove excess water before benzyl alcohol (10 mL) was passed over the column under a pressure of N_2. N_2 was then blown over the resin for 5 min to remove excess

solvent and facilitate its removal from the column. Approximately 300 mg (the amount necessary to make a thick slurry of resin in the desired amount of solvent) of the resin was added to the oxazolidionone **53** (0.0296 g, 0.097 mmol) and the flask was evacuated and backfilled with N_2 four times. Benzyl alcohol (1.0 mL) was added and the heterogeneous mixture heated to 100 °C for 9 h, at which time TLC analysis indicated a complete reaction. The mixture was cooled to RT and filtered over Celite with MeOH. Rotary evaporation of the volatile organic material followed by Kugelrohr distillation (0.1 mm Hg, 50 °C) to remove benzyl alcohol afforded a pale yellow oil. Flash chromatography (gradient 2–12% MeOH/CH_2Cl_2) provided a pale yellow solid (19.3 mg, 51%). R_f=0.25 (10% MeOH/CH_2Cl_2); m.p. 95–97 °C; $[\alpha]_D^{24}$ = +25.51 (c=1.0, CH_2Cl_2); ^{1}H (500 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 10H), 4.67 (d, J=12.0 Hz, 1H), 4.57 (d, J=12.0 Hz, 1H), 4.53 (s, 2H), 4.08 (dd, J=5.5, 4.0 Hz, 1H), 3.80–3.78 (m, 2H), 3.22 (q, J=5.5 Hz, 1H), 3.10 (t, J=5.0 Hz, 1H), 3.03 (brs, 4H), 1.68–1.64 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.0, 137.8, 128.54, 128.53, 127.91, 127.88, 127.80, 127.80, 88.0, 79.0, 73.3, 72.0, 71.0, 69.7, 66.2, 63.6, 60.7, 36.1 ppm; IR (neat): $\tilde{\nu}$ = 3357 cm^{-1}; HRMS (EI): m/z: calcd for $C_{22}H_{30}NO_5$: 388.2124, found 388.2136 [M+H$^+$].

Australine hydrochloride (55): Mesyl chloride (6.2 mg, 0.054 mmol) was added to a solution of **54** (19.0 mg, 0.049 mmol) and Et_3N (10.9 mg, 0.11 mmol) in CH_2Cl_2 (1.0 mL) at −30 °C. The temperature was maintained for 1 h then allowed to slowly warm to 0 °C over 1 h then to RT for 20 min. The solvent was removed in vacuo and flash chromatography (gradient 2 to 10% MeOH, CH_2Cl_2) afforded a pale yellow oil (13.4 mg, 74%). R_f=0.36 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{24}$ = −9.9240 (c=1.0, CH_2Cl_2); ^{1}H (500 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 10H), 4.71 (d, J=12.0 Hz, 1H), 4.60 (d, J=12.0 Hz, 1H), 4.56 (d, J=12.0 Hz, 1H), 4.53 (d, J=12.0 Hz, 1H), 4.28 (dd, J=7.0, 6.0 Hz, 1H), 4.16–4.12 (m, 2H), 3.63–3.54 (m, 2H), 3.45 (dd, J=5.5, 4.0 Hz, 1H), 3.20–3.12 (m, 1H), 2.91 (q, J=6.5 Hz, 1H), 2.77–2.72 (m, 1H), 1.99–1.90 ppm (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.5, 138.1, 128.5, 128.45, 127.82, 127.80, 127.72, 127.70, 81.4, 81.1, 73.5, 73.0, 72.5, 72.1, 71.1, 70.6, 52.4, 36.9 ppm; IR (neat): $\tilde{\nu}$ = 3385 cm^{-1}; HRMS (EI): m/z: calcd for $C_{16}H_{20}NO_4$: 278.1392, found 278.1394 [M−PhH$_2^+$].

Based on the previously reported procedure,[25] palladium chloride (8.0 mg) was added to a solution of the dibenzyl ether (8.0 mg, 0.022 mmol) in MeOH (1 mL) and the heterogeneous mixture was stirred rapidly for 20 min. The flask was evacuated under a gentle vacuum and backfilled with H_2 (5×), then allowed to stir for 1.25 h. The crude reaction mixture was then evacuated under a gentle vacuum and backfilled with air (5×) and filtered over Celite with MeOH. Evacuation of the solvent provided an extremely pure sample of the title compound as an opaque white oil (4.8 mg, 98%) that satisfactorily matched all previously reported data.[23f] $[\alpha]_D^{24}$ = +22.35 (c=0.3, H_2O), lit.[23f] $[\alpha]_D^{20}$ = +22.2 (c=0.50, H_2O); ^{1}H (600 MHz, D_2O reference set to 4.78 ppm): δ = 4.68 (dd, J=6.6, 4.2 Hz, 1H), 4.84 (t, J=7.8 Hz, 1H), 4.15 (dd, J=10.2, 7.8 Hz, 1H), 3.99 (dd, J=13.2, 3.6 Hz, 1H), 3.92–3.88 (m, 2H), 3.81 (ddd, J=11.4, 7.8, 3.0 Hz, 1H), 3.42–3.35 (m, 2H), 2.33–2.29 (m, 1H), 2.26–2.19 ppm (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 75.4, 72.6, 71.4, 70.6, 68.0, 55.7, 52.1, 34.3 ppm; IR (neat): $\tilde{\nu}$ = 3355 cm^{-1}.

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