Construction of Consecutive Chiral Non-Racemic Quaternary and Tertiary Carbon Centers: A Short Synthetic Route to (−)-Acetomycin

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Regio- and diastereoselective nucleophilic substitution of 2-methylacetoacetate with a chiral non-racemic π-allyl Pd complex creates consecutive chiral non-racemic quaternary and tertiary carbon centers. σ-Bond formation between the *re*-face of the π-allyl Pd complex and the *re*-face of the enol acetoacetate was controlled by the *o*-(diphenylphosphanyl)-arylcarboxylic acid ligand selectively. (−)-Acetomycin was synthesized in seven steps using this key approach.

Introduction

Creation of a chiral non-racemic quaternary carbon center is one of the challenging tasks in organic synthesis.[1] Attempts to prepare a chiral non-racemic quaternary carbon center have been made by using chiral ligands in catalytic reactions as well as chiral auxiliaries in stoichiometric reactions, such as in the alkylation reaction,[2] Diels−Alder reaction,[3] Heck reaction[4] and a few others.[5] However, the lack of a general method for the preparation of consecutive chiral non-racemic quaternary and tertiary carbon centers led us to undertake this study.

Pd-catalyzed asymmetric allylic alkylation is a powerful and widely used method for the carbon-carbon bond forming reaction that generates, simultaneously, a new stereogenic carbon center.[6] For the construction of a chiral non-racemic quaternary carbon center, investigations have been performed on this reaction.[7] However, the reaction of α-substituted unsymmetrical β-diketones or α-substituted β-keto esters with non-chiral unsymmetric or chiral allylic acetate generally gives a mixture of regio- and stereoisomers with poor selectivity. If a chiral non-racemic allyl acetate is employed,[8] as shown in Scheme 1, the remaining problems for this reaction would boil down to the control of regio- and diastereoselectivities, because the allylic alkylation reaction proceeds stereospecifically with net retention of the stereochemistry. In this communication, we report the first successful regio- and diastereo-control of Pd-catalyzed allylic alkylation of chiral non-racemic allyl acetate with an α-substituted β-keto ester, giving an optically pure β-keto ester, having consecutive quaternary and adjacent tertiary carbon centers.

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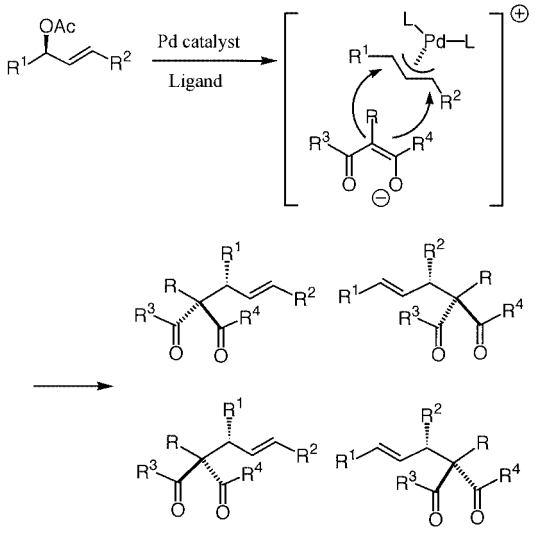


Scheme 1. Pd catalyzed allylic alkylation of α-substituted β-diketone with chiral non-racemic allyl acetate

Results and Discussion

We chose (*R*)-2-acetoxy-4-phenyl-3-butene (**1**)[9] as a chiral non-racemic allyl acetate and ethyl 2-methylacetoacetate (**2**) as a counter nucleophile. First, we examined the Helmchen−Pfaltz oxazolidine ligands.[10] When (*R*)-*ip*-Phox (see Figure 1) was used with a catalytic amount of $Pd(OAc)_2$ with NaHMDS as a base in 1,4-dioxane, the regioisomer **3** was exclusively yielded over the alternative regioisomer **4** (Scheme 2). The diastereomeric ratio of **3** was 42:58, as determined by proton NMR spectroscopy (entry 1).

Mismatching of the regio- and stereoselectivity of **1** with (*S*)-*ip*-Phox (Figure 1) gave a mixture of **3** and **4** in a 41:59 ratio, each regioisomer being obtained as approximately a 1:1 mixture of *R* and *S* diastereomers. The results for other

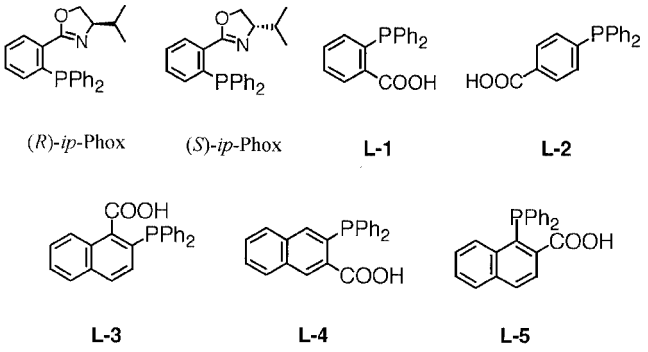
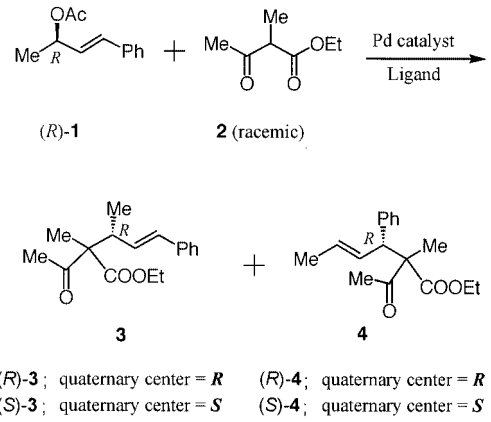
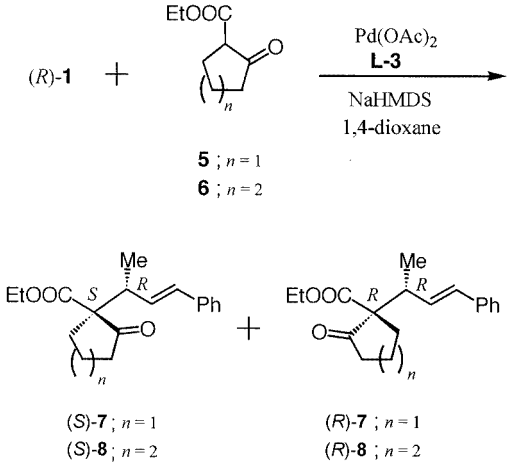


Figure 1. Structures of phosphane ligands



Scheme 2. Reaction of ethyl 2-methylacetoacetate with (*R*)-2-acetoxy-4-phenyl-3-butene

conditions, including other ligands[11] and Pd sources, are depicted in Table 1. Although the use of $Pd(PPh_3)_4$ or a combination of $Pd(OAc)_2$ and PPh_3 gave a single regioisomer **3**, the diastereoselectivities were about 1:1 (entries 3 and 4). These poor diastereoselectivities were dramatically improved using a carboxylic acid ligand. When *o*-(diphenylphosphanyl)benzoic acid **L-1** (Figure 1) was employed as a ligand (entry 5), the diastereoselectivity ratio was increased remarkably to 94:6[12] with perfect regioselectivity, and **3** was obtained in 86% yield. Diastereoselectivity and reactivity were decreased by the use of Li and K salts (entries 6 and 7). On the other hand, the corresponding *para* isomer **L-2** was poorly diastereoselective (entry 8). An *ortho* carboxylic acid moiety was found to be important for the face selectivity of enolate. (Diphenylphosphanyl)naphthoic acids, **L-3** and **L-4**, both had an excellent regioselectivity of over 99:1 and a diastereoselectivity of 94:6 (Scheme 3). Their chemical yields were fairly good, 86 and 87%, respectively. When 1-(diphenylphosphanyl)-2-naphthoic acid **L-5** was used, it only produced a 19% yield of **3** as a 1:1 mixture of the diastereomers. Therefore, the phosphanyl group located at the β-position on the naphthalene ring is required for good chemical reactivity and high diastereoselectivity for this reaction.



Scheme 3. Reaction of 2-ethoxycarbonylcyclicketones with (*R*)-**1**

The reaction of **1** with 2-ethoxycarbonylcyclopentanone (**5**) proceeded regio- and diastereoselectively to give (*S*)-**7** over (*R*)-**7** with a 92:8 ratio in 75% yield. Similarly, 2-ethyoxycarbonylcyclohexanone (**6**) gave (*S*)-**8** predominantly over (*R*)-**8** with a 93:7 ratio in 77% yield. In these

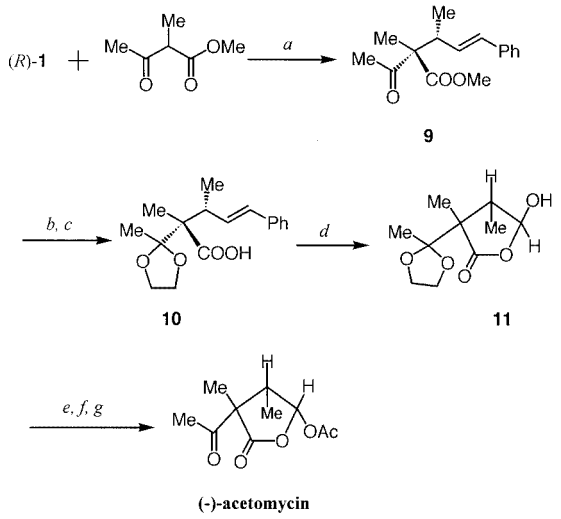
Table 1. Diastereoselective allylic alkylation of (*R*)-**1** with ethyl 2-methylacetoacetate[a]

Entry	Pd catalyst[b]	Ligand[c]	Base[d]	SM: Products[e]	Regioselectivity[f] **3:4**	Diastereoselectivity[f] **(*S*)-3:(*R*)-3**
1	$Pd(OAc)_2$	(*R*)-*ip*-Phox	NaHMDS	7:93	>99:1	42:58
2	$Pd(OAc)_2$	(*S*)-*ip*-Phox	NaHMDS	1:>99	41:59[g]	50:50
3	$Pd(PPh_3)_4$	none	NaHMDS	3:97	>99:1	55:45
4	$Pd(OAc)_2$	PPh_3	NaHMDS	27:73	>99:1	55:45
5	$Pd(OAc)_2$	L-1	NaHMDS	1:>99	>99:1	94:6
6	$Pd(OAc)_2$	L-1	LiHMDS	14:86	>99:1	85:15
7	$Pd(OAc)_2$	L-1	KHMDS	7:93	>99:1	69:31
8	$Pd(OAc)_2$	L-2	NaHMDS	1:>99	95:5	53:49
9	$Pd(OAc)_2$	L-3	NaHMDS	1:>99	>99:1	94:6
10	$Pd(OAc)_2$	L-4	NaHMDS	1:>99	>99:1	94:6
11	$Pd(OAc)_2$	L-5	NaHMDS	66:34	>99:1	48:52

[a] The reaction was carried out in 1,4-dioxane at room temperature. [b] 5 mol % of Pd was used. [c] 10 mol % of phosphane was used. [d] In each reaction, 1.4 equiv. of base and 1.5 equiv. of ethyl 2-methylacetoacetate were used. [e] The reaction was stopped after 12 h, even if starting material remained. When the reaction went to completion the yield of products was usually 80−95%. [f] The ratio was determined from the proton NMR spectrum of the crude products and the values given are an average of two or three experiments. [g] The diastereoselectivity of **4** was approximately 1:1.

Pd-catalyzed diastereoselective σ-bond forming reactions, it is noteworthy that the face selectivity of a β-keto ester enolate was highly controlled by a simple *o*-(diphenylphosphanyl)arylcarboxylic acid.

Acetomycin was isolated from *Streptomyces ramulosus sp.* in 1958 by Prelog et al.[13] It is a rather small molecule (M_r 214) but possesses unique and potent *anti*-tumor activity.[14] In addition, its highly oxygenated structure, having three chiral centers located consecutively on the γ-lactone ring, is particularly attractive for synthetic chemists. Although several total syntheses, including ours, have been reported so far,[15] these methods are rather tedious or lack flexibility for the preparation of its analogues. The consecutive quaternary and tertiary carbon centers of the molecule are good synthetic targets for demonstrating the above synthetic method. The synthesis is outlined in Scheme 4.



Scheme 4. Synthesis of (−)-acetomycin; reagents & conditions: a) cat. $Pd(OAc)_2$, 2-(diphenylphosphanyl)naphthoic acid, NaHMDS, 1,4-dioxane; b) cat. CSA, ethylene glycol, benzene, reflux; c) $LiSC_{12}H_{25}$, HMPA; d) O_3, CH_2Cl_2, then Me_2S; e) MsCl, Et_3N, CH_2Cl_2; f) AcOK, dibenzo-18-crown-*O*-6, toluene, reflux; g) TsOH, acetone

In the first step, allylation of methyl 2-methylacetoacetate[16] with (*R*)-**1** using the ligand **L-3** gave **9** in 95% yield with a 93:7 ratio. Protection of the carbonyl group with ethylene glycol in the presence of CSA followed by hydrolysis of methyl ester with odorless thiol lithium salt[17] gave the carboxylic acid **10** in 83% yield in two steps. After ozonolysis of the alkenyl bond, the carboxylic acid was immediately cyclized to give lactol **11** in 95% yield. Replacement of the anomeric hydroxy group at the β-position with an acetoxy group was achieved with inversion of the configuration via its methanesulfonate by the nucleophilic attack of acetoxy anion activated by dibenzo-18-crown-*O*-6.[15b] The desired acetate was obtained in 51% yield. Finally, deprotection of the acetal under acidic conditions gave (−)-acetomycin in 82% yield. All of the physical and spectroscopic data, including melting point (mp, 110−111 °C) and specific rotation $\{[\alpha]_D^{22} = -156$ (c = 0.43, EtOH)$\}$, are in good accordance with those of the natural product.[18] This method has considerably shortened the reaction steps.[19]

Conclusion

In conclusion, fully carbon-substituted consecutive quaternary and tertiary carbon centers were constructed with high regio- and stereoselectivity by a Pd catalyzed allylic alkylation reaction. The utility of this reaction was demonstrated by producing the shortest asymmetric synthesis of (−)-acetomycin so far achieved. We are now investigating the details of this reaction mechanism.

Experimental Section

Representative Experimental Procedure for Pd Catalyzed Allylic Alkylation Reaction: (*R*)-2-Acetoxy-4-phenyl-3-butene (**1**; 190 mg, 1.0 mmol) and ethyl 2-methylacetoacetate (**2**; 216 mg, 1.50 mmol) were added to a stirred solution of 2-(diphenylphosphanyl)benzoic acid (30.6 mg, 0.10 mmol) and $Pd(OAc)_2$ (11.2 mg, 0.050 mmol) in anhydrous 1,4-dioxane (7.4 mL). NaHMDS (1.40 mmol, 1.4 mL of 1.0 M in THF) was slowly added dropwise at 0 °C, and the resultant mixture allowed to warm up to room temperature over 12 h. The standard work up and purification of the crude product by silica gel chromatography gave **3** (237 mg) in 86% yield as a colorless oil **(*R*)-3:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35−7.20 (m, 5 H), 6.43 (d, J = 15.8 Hz, 1 H), 6.05 (dd, J = 15.8, 8.6 Hz, 1 H), 4.22 (q, J = 7.1 Hz, 2 H), 3.23 (m, 1 H), 2.17 (s, 3 H), 1.35 (s, 3 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.13 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.9, 172.0, 137.2, 131.4, 130.3, 128.5, 127.4, 126.3, 63.5, 61.3, 41.1, 26.9, 16.4, 16.0, 14.1 ppm. HRMS(EI) calcd. for $C_{17}H_{22}O_3$ [M^+]: m/z = 274.1569; found 274.1567.
(*S*)-3: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43−7.19 (m, 5 H), 6.42 (d, J = 15.8 Hz, 1 H), 6.15 (dd, J = 15.8, 8.4 Hz, 1 H), 4.15 (q, J = 7.1 Hz, 2 H), 3.24 (m, 1 H), 2.19 (s, 3 H), 1.36 (s, 3 H), 1.23 (t, J = 7.1 Hz, 3 H), 1.07 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.0, 171.9, 137.3, 131.3, 130.7, 128.5, 127.3, 126.2, 63.7, 61.7, 41.0, 26.8, 15.7, 15.2, 14.1 ppm.

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