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Application of Pd(0)-Catalyzed Intramolecular Oxazine Formation to the Efficient Total Synthesis of (–)-Anisomycin

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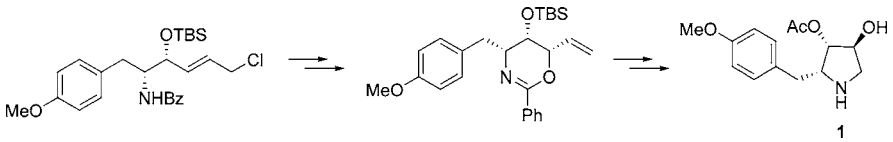
ABSTRACT



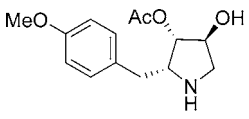
The enantioselective total synthesis of (–)-anisomycin, a potent antibiotic agent, has been achieved. The key steps are a Pd(0)-catalyzed stereoselective intramolecular oxazine formation from D-tyrosine and pyrrolidine formation by catalytic hydrogenation of the oxazine.

The antibiotic (−)-anisomycin (**1**) (Figure 1) was first isolated from the fermentation broths of *Streptomyces griseolous* and *Streptomyces roseochromogens* by Sobin and Tanner in 1954[1] and has since been obtained from *Streptomyces* sp. No. 638 and *SA* 3097.[2] It was reported to possess the 2*S*,3*S*,4*S* absolute configuration.[3]

(−)-Anisomycin exhibits strong and selective activity against pathogenic protoza and fungi.[4] It has been used clinically for treatment of both amoebic dysentery and *Trichomonas vaginitis* and as a fungicide to eradicate bean mildew and to inhibit other pathogenic fungi in plants.[5] It has also been shown to exhibit antiviral and antitumor activities due to apoptotic activity.[6]

Because of its promising biological profile, much effort has been devoted to the development of an efficient synthesis of this antibiotic and its deacetyl analogue. More than 20 syntheses of anisomycin and its analogues have been reported in the past several years. However, many of the published procedures suffer from inefficient protecting group chemistry in the later stages.[7]

Recently, we have described a new Pd(0)-catalyzed procedure for the stereoselective formation of an oxazine ring from a γ-allylic benzamide having a benzoyl substituent



(-)-Anisomycin (1)

Figure 1. (−)-Anisomycin.

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(1) Sobin, B. A.; Tanner, F. W. *J. Am. Chem. Soc.* **1954**, *76*, 4053.
(2) (a) Ishida, S.; Yamada, O.; Futatsuya, F.; Ito, K.; Yamamoto, H.; Munakata, K. *Proc. Int. Congr. IAMS 1st* **1974**, *3*, 641. (b) Hosoya, Y.; Kameyama, T.; Naganawa, H.; Okami, Y.; Takeuchi, T. *J. Antibiot.* **1993**, *46*, 1300.
(3) Wong, C. M. *Can. J. Chem.* **1968**, *46*, 1101.
(4) Jimenez, A.; Vazquez, D. In *Antibiotics*; Hahn, F. E., Ed.; Springer-Verlag: Berlin, 1979; pp 1−19. Grollman, A. P. *J. Biol. Chem.* **1967**, *242*, 3226.
(5) (a) Schumacher, D. P.; Hall, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 6076. (b) Han, G.; LaPorte, M. G.; McIntosh, M. C.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 9483.

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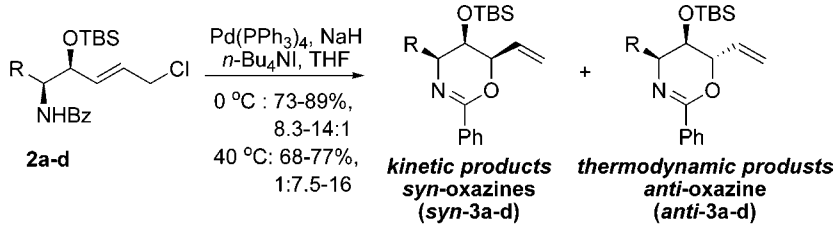
Scheme 1



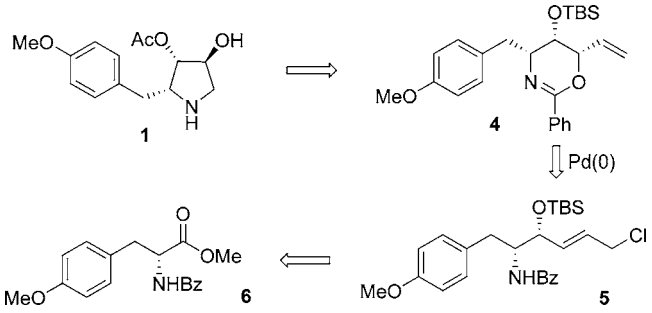
R = (a) $C_6H_5CH_2^-$, (b) $(CH_3)_2CH^-$, (c) $(CH_3)_2CHCH_2^-$, (d) $C_6H_{11}CH_2^-$

as an N-protection group in the presence of $Pd(PPh_3)_4$, NaH, and *n*-Bu_4NI. Unlike other palladium-catalyzed reactions, the diastereoselectivity of oxazine ring formation is predominantly controlled by the temperature.[8]

Our study into intramolecular oxazine formation from **2a**−**d** has shown that the stereoselectivity of these cyclizations can be critically dependent upon whether the reaction temperature results in kinetic or thermodynamic control of the products (Scheme 1). Oxazines *syn*-**3a**−**d** require conditions giving kinetic control (0 °C), whereas *anti*-**3a**−**d** are observed under thermodynamic control (40 °C).

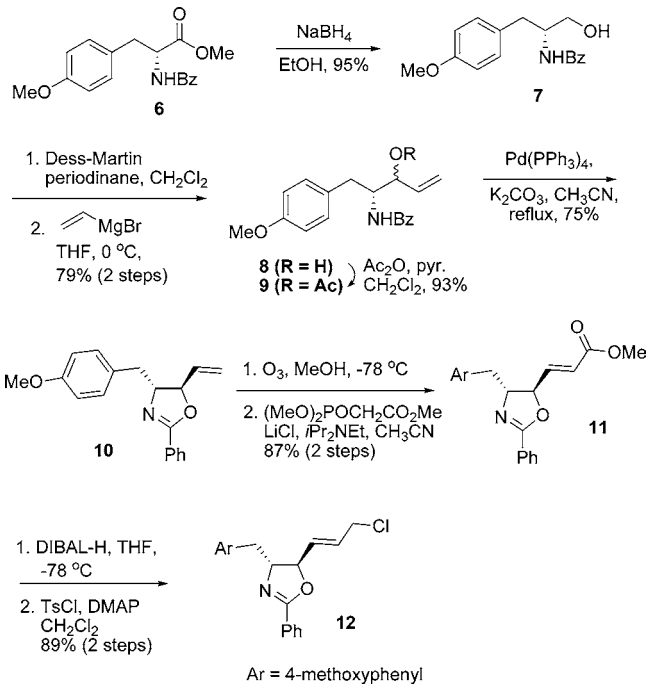
We envisioned that this method could be utilized to set the three contiguous stereocenters of (−)-anisomycin (**1**). The pendant vinyl group of oxazine **4** could be converted to the corresponding aldehyde, which could be employed in formation of the pyrrolidine ring by catalytic hydrogenation of oxazine. We now report an enantioselective synthesis of **1** in accordance with these strategies. Our retrosynthetic analysis is displayed in Scheme 2.

Scheme 2. Retrosynthetic Analysis



Our initial efforts in the synthesis of the requisite *trans*-oxazoline allyl chloride **12** commenced with the protected *N*-benzoyl-D-tyrosine methyl ester (**6**) as shown in Scheme 3. Reduction of the ester **6** with sodium borohydride in ethanol furnished amino alcohol **7** in 95% yield. Oxidation of the alcohol with Dess−Martin periodinane gave the corresponding aldehyde, which was reacted with vinylmagnesium bromide in THF at 0 °C to afford allyl alcohol **8** as a 1.1:1 mixture of *syn*/*anti* isomers (^{1}H NMR) in 79% yield. Acetylation of the hydroxyl group yielded the secondary allylic acetate, and the palladium-catalyzed oxazoline ring formation of the allylic acetate **9** gave the desired *trans*-oxazoline **10** as a single diastereomer in good yield (75%).[9]

Scheme 3



Ozonolysis of the olefin **10** and subsequent Horner−Wardsworth−Emmons reaction afforded the α,β-unsaturated ester **11** with good *E*/*Z* selectivity (>15:1, ^{1}H NMR). Reduction of compound **11** by DIBAL-H at −78 °C and conversion of this allylic alcohol to the chloride under TsCl/DMAP conditions gave the desired allyl chloride **12** in good yield (89%).

(6) (a) Stadheim, T. A.; Kucera, G. L. *Leuk. Res.* **2002**, *26*, 55. (b) Torocsik, B.; Szeberenyi, J. *Biochem. Biophys. Res. Commun.* **2000**, *278*, 550. (c) Lee, Y. S.; Wurster, R. D. *Cancer Lett.* **1995**, *93*, 157.

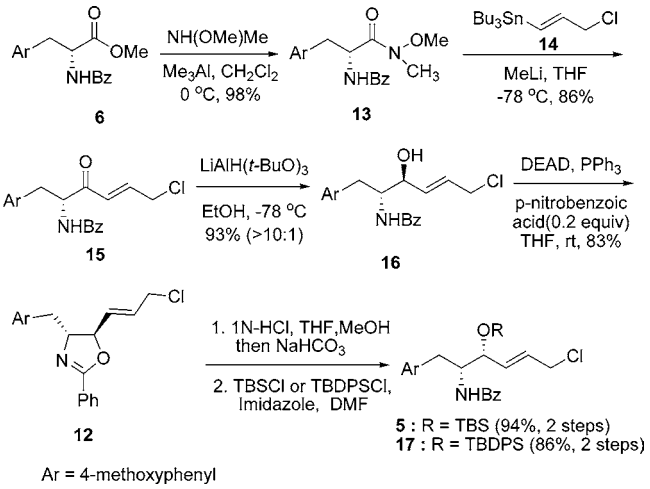
(7) (a) Kim, J. H.; Crutis-Long, M. J.; Seo, W. D.; Ryu, Y. B.; Yang, M. S.; Park, K. H. *J. Org. Chem.* **2005**, *70*, 4082 and references therein. (b) Hulme, A. N.; Rosser, E. M. *Org. Lett.* **2002**, *4*, 265 and references therein.

(8) Joo, J. E.; Lee, K. Y.; Pham, V. T.; Ham, W. H. *Eur. J. Org. Chem.* **2007**, 1586.

(9) (a) Lee, K. Y.; Oh, C. Y.; Ham, W. H. *Org. Lett.* **2002**, *4*, 4403. (b) Lee, K. Y.; Kim, Y. H.; Oh, C. Y.; Ham, W. H. *Org. Lett.* **2000**, *2*, 4041. (c) Lee, K. Y.; Kim, Y. H.; Park, M. S.; Oh, C. Y.; Ham, W. H. *J. Org. Chem.* **1999**, *64*, 9450.

However, the preparation of allyl chloride **12** was plagued by protecting group manipulations and functional group interconversions, leading to synthetic inefficiency. Consequently, a new method for synthesizing **12** was conceived (Scheme 4).

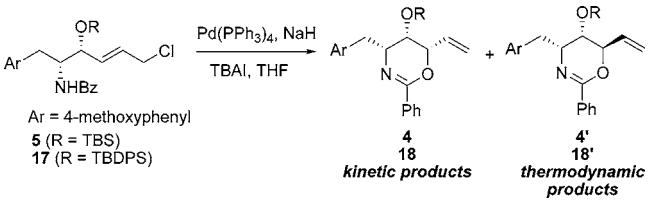
Scheme 4



The ester **6** was readily converted into Weinreb amide **13** by treatment with *N*,*O*-dimethylhydroxylamine in the presence of trimethylaluminum in 98% yield. Reaction of Weinreb amide **13** with vinyltin **14** and MeLi in THF at −78 °C gave α,*β*-unsaturated ketone **15** in 86% yield. To investigate the anti-selective reduction, amino ketone **15** was treated with various reducing agents, and we found that reaction with lithium tri-*tert*-butoxyaluminohydride in ethanol at −78 °C gave the desired alcohol **16** as the major compound in good yield (93%) with excellent stereoselectivity (anti/syn = 10:1).[10] A *p*-nitrobenzoic acid catalyzed Mitsunobu-type reaction of *anti*-amino alcohol **16** gave the *trans*-oxazoline **12** in good yield (83%). The spectroscopic data of the resulting oxazoline **12** were identical to those of oxazoline **10**. Subsequent acid-catalyzed hydrolysis of the oxazolines, followed by the addition of sodium bicarbonate to increase the pH of the reaction mixture to 9.0, furnished the *syn*-amino alcohol. Protection of the resulting alcohol by TBSCl or TBDPSCl afforded the cyclization precursors **5** and **17** in excellent yield.

Under the conditions of $Pd(PPh_3)_4$, NaH, and *n*-Bu_4NI in THF at 0 °C, the stereoselective intramolecular cyclization of allyl chloride **5** afforded the *syn*-oxazine **4** as a 15:1 mixture of syn/anti isomers (^{1}H NMR) in good yield (Table 1, entry 1). The reaction at room temperature showed a different selectivity, where the anti adduct (**4′**) was obtained as the major isomer (entry 2). When the reaction temperature was increased to 50 °C, a better diastereoselectivity was observed (1:9 mixture of the syn/anti isomer, entry 3). In the case of the more bulky TBDPS group, the syn isomer was formed predominantly (entry 4). It is interesting that the palladium-catalyzed reaction was so dependent on temperature. Starting from **5**, both syn and anti isomers can be stereoselectively prepared simply by changing the reaction temperature: syn under kinetic control (0 °C) and anti under thermodynamic control (50 °C). The configuration of the newly generated chiral center in oxazine **4** could not be deduced from the NMR spectra but could be anticipated to possess the syn configuration on the basis of previous results.[8,11]

Table 1. Oxazine Formation Catalyzed by Pd(0)

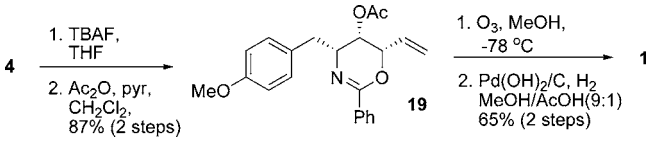


entry	substrate	temp (°C)	time (h)	yield[a] (%)	ratio[b] (syn/anti)
1	5	0	12	79	15:1
2	5	rt	12	81	1:5
3	5	50	12	68	1:9
4	17	0	12	72	>30:1

[a] Yields refer to the isolated and mixture products. [b] Ratio was determined by ^{1}H NMR.

Completion of the synthesis of (−)-anisomycin was achieved via deprotection of the silyl ether of the oxazine **4** and acetylation of this alcohol (Scheme 5). Ozonolysis of the oxazine **19** gave the corresponding aldehyde. Hydrogenolysis of the aldehyde in a 9:1 MeOH/AcOH mixture was performed under 70 psi of H_2 catalyzed by $Pd(OH)_2$/C at ambient temperature. Under these conditions, we achieved not only hydrogenolysis of the oxazine moiety but also cyclization of the intermediate aminoaldehyde to **1** as a single isomer.

Scheme 5



The synthetic compound was spectroscopically in good agreement with the natural and synthetic (−)-anisomycin. The optical rotation of our compound **1**, $[\alpha]_D^{25}$ −29.0° (*c* 1.0, MeOH), compared to the reported value,[12] $[\alpha]_D^{23}$ −30.4° (*c* 1.0, MeOH), confirms the absolute configuration.

(10) (a) Pham, V. T.; Joo, J. E.; Tian, Y. S.; Oh, C. Y.; Ham, W. H. *Arch. Pharm. Res.* **2007**, *30*, 22. (b) Hoffman, R. V.; Maslouh, N.; Lee, F. C. *J. Org. Chem.* **2002**, *67*, 1045.

(11) Compound **4** has a pattern almost similar with the previously reported benzyl oxazine compound at TLC and ^{1}H NMR. The proton of terminal olefin and H^5 have peaks at 6.0 and 4.1 ppm. In addition, the coupling constants of the newly generated chiral center (H^5−H^6) of compound **4** have the same value of 1.5 Hz compared to that of all *syn*-oxazine compounds previously reported.

In summary, we report a new asymmetric synthetic method for (−)-anisomycin utilizing oxazine **4**. The net result is a synthesis having a longest linear sequence of 11 steps and proceeding in 27% yield. The key features in this strategy are the stereoselective intramolecular oxazine formation by palladium(0) and pyrrolidine formation by catalytic hydrogenation of the oxazine.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 1069.