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通过[2,3]-Wittig 重排合成烯丙基-甲基-N-泛酸酰胺

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摘要 Allyl-methyl-N-Pantothenamide **1**，具有手性季碳和邻位仲醇结构片段的抗菌剂，可以巧妙通过[2,3]-Wittig 重排和钯催化的甲酸还原构建了其分子骨架。以 10 步反应制备了 allyl-methyl-N-Pantothenamide **1** 。

关键词 [2,3]-Wittig 重排; N-Pantothenamide; 手性季碳; 抗菌剂;

A novel synthetic route to access allyl-methyl-N-pantothenamide *via* [2,3]-Wittig rearrangement.

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Abstract The synthetic route of allyl-methyl-N-Pantothenamide **1** featuring [2,3]-Wittig rearrangement and palladium catalyzed formate reduction to assemble the requisite quaternary carbon with adjacent secondary alcohol has been reported. Our strategy present a facile synthetic route to access allyl-methyl-N-Pantothenamide **1** in 10 steps, which also provide a novel inspiration to construct chiral quaternary carbon *via* asymmetrical [2,3]-Wittig rearrangement.

Keywords [2,3]-Wittig rearrangement; N-Pantothenamide; chiral tertiary carbon; antimicrobial;

1 Introduction

The N-substituted pantothenamide antimetabolites are analogs of pantothenic acid, the coenzyme A(CoA) precursor(Figure 1)[1]. These compounds had been utilized as antimicrobial agents, and as probe of the active site of pantothenate kinase. N-Pentylpantothenamide (N5-Pan), the benchmark molecule in this field, had been shown to participate in several steps of CoA synthetic reactions, leading to the formation of the inactive CoA analog ethyldethia-CoA, which irreversibly inhibited the acyl carrier protein (ACP) of the fatty acid biosynthetic machinery[2]. One of the promising derivatives reported was methyl-allyl-N-Pantothenamide **1** with a *MIC* of 3.2 uM against S. *aureus* and *MRSA*, which had clear superiority in antibacterial activity assays[3, 4]. The intriguing chemical structure and potential biological activity of N-Pentylpantothenamide have spurred considerable interests among the chemistry community.

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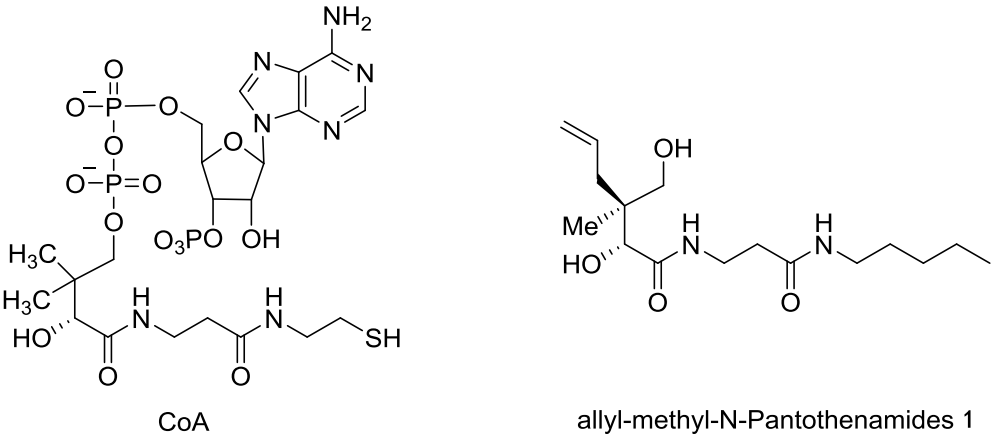
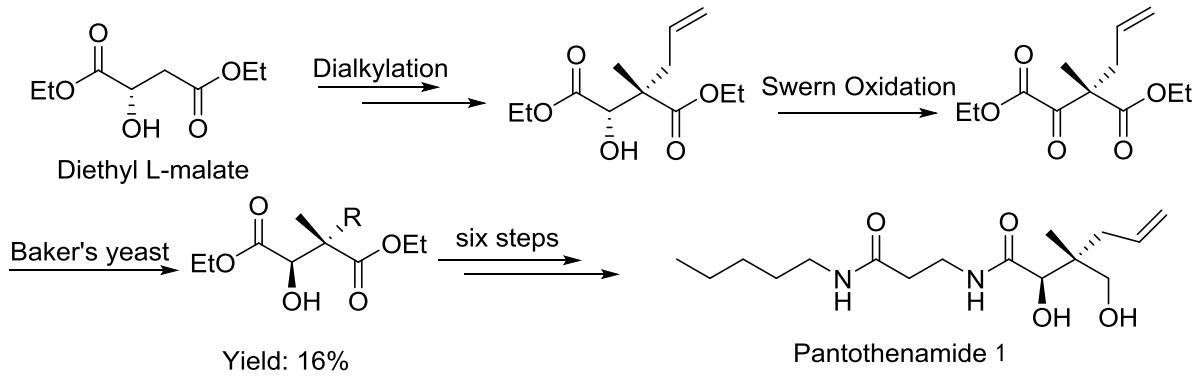


Figure 1: Chemical structure of CoA and Pantothenamide **1**

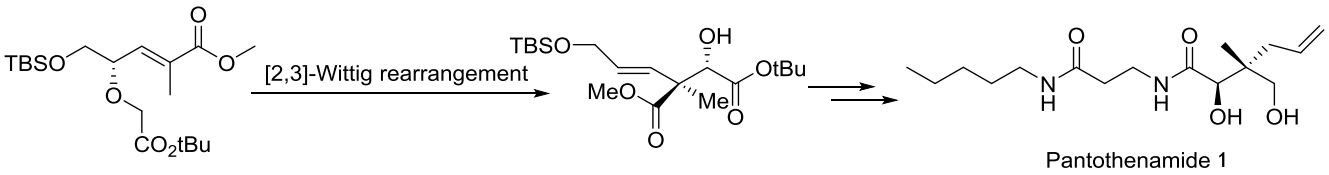
Karine Auclair et al[3, 4]. (Scheme 1) have recently disclosed the stereochemical synthetic route to Pantothenamides **1** by employing Baker's yeast to reduce the dialkyl substituted α-ketomalonates. As shown below, the Frater-Seebach method[5] of alkylating chiral β-hydroxy esters was used to generate the geminal dialkyl groups. Followed by Swern oxidation of the resulting secondary alcohol, Baker's yeast was utilized to reduce the oxosuccinate, leading to the desired quaternary carbon with vicinal secondary alcohol moiety. Although Baker's yeast gave excellent diastereoselectivity (*dr*>98:2, with one exception at 80:20), the most significant limitations of this methodology consist in specific condition (Baker's yeast), difficulties in operation (precise temperature control) , as well as the moderate yield and the decreased diastereoselcetivity by replacing of the bulky alkyl substitutes (hexyl, isobutyl and ethyl groups).



Scheme 1: Synthesis of Pantothenamide **1** by Karine Auclair

With control of both absolute and relative configurations, the solution was challenging, so an urgent transformation need to exploit to restore the new bonds onto a bulky steric skeleton. Asymmetric [2,3]-Wittig rearrangement was an intriguing method by which to provide chiral building blocks for synthesis of natural products[6-8]. This type of asymmetric version destroys the original chirality while simultaneously creating new ones, with considerable stereopredictability. These valuable features exactly satisfy our requirement to create the chiral quaternary carbon with vicinal secondary alcohol moiety in one step, by virtue of the proper choice of trisubstituted allylic ethers. Actually, several asymmetric versions of the enolate [2,3]-Wittig process have been developed, whereas the trisubstituted allylic ethers has been rarely reported to be a precursor yet[8].

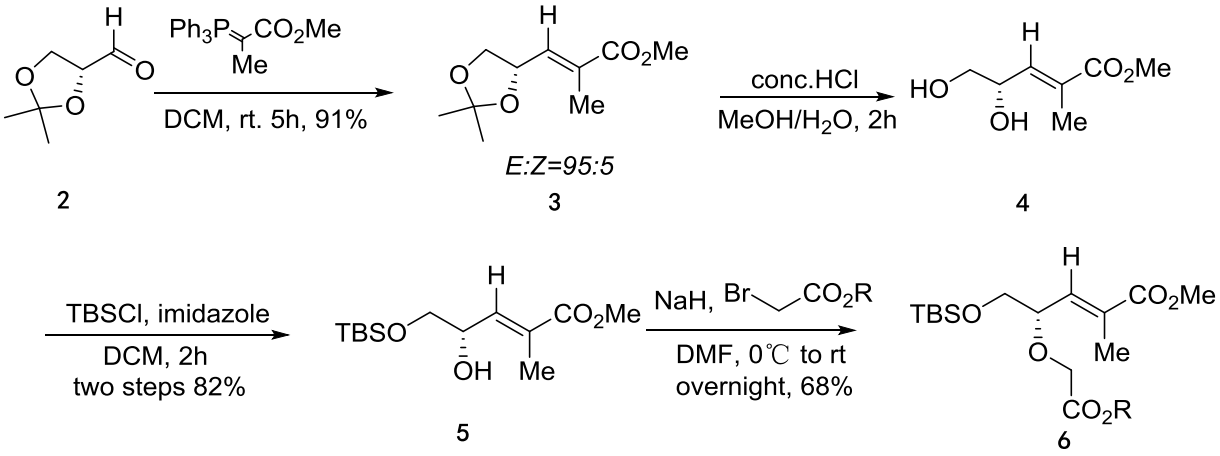
Inspired by our recent advances in the enantioselective synthesis of tertiary alcohol via [2,3]-Meisenheimer rearrangement[9], we envisioned that [2,3]-Wittig rearrangement would be potentially served to assemble this sterically congested tertiary carbon. Herein we report our efforts on the development of the facile strategy that allowed the total synthesis of **1** in 10 steps.



Scheme 2: Synthetic route of Pantothenamide **1** by [2,3]-Wittig rearrangement

2 Results and discussion

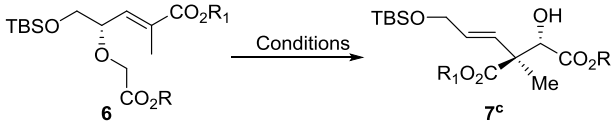
The desired (*E*)-olefin **3** was generated from commercially available (*S*)-Glyceraldehye acetonide in 91% yield *via* Wittig coupling. Deprotection of olefin **3** and subsequent selective TBS protection of 1,2-diol **4** to afforded alcohol **5**, which was treated with alkyl 2-bromoacetate to provide ether **6**, the precursor of [2,3]-Wittig rearrangement, in 68% yield (R=Me).

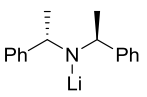


Scheme 3: Synthesis of precursor **6**

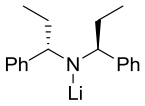
In an attempt to access the key rearrangement intermediate, 4-(2-methoxyl-2-oxoethoxy)-enoate **6** (R=Me) was selected as the model substrate. Initially, 2.2 equivalent lithium diisopropylamide was added into ester **6** in THF solution in the present of hexamethylphosphoric triamide (HMPA) while the reaction mixture turned from yellow to dark red. We were pleased to found that the rearrangement product **7** bearing quaternary carbon was obtained in 47.1% isolated yield with the 27:73 *dr* (Table 1,Entry 1), whereas this value was much lower than that achieved by Baker's yeast[3]. The moderate yield maybe caused by sort of byproducts which couldn't be identified by NMR. The screening of strong bases showed that lithium 2,2,6,6-Tetramethylpiperidine(TMPLi), the more sterically hindered base, led to a slightly higher diastereoselectivity and isolated yield than other achiral base(LDA, NaHMDS) (Table 1, Entry 2-3). When switching achiral bases to chiral lithium (S)-bis((S)-1-phenylethyl)amine and lithium (S)-bis((S)-1-phenylpropyl)[10], unfortunately, the yield and diastereoselectivity slightly decreased(Table 1, Entry 4-5) and lithium (S)-2-(methoxymethyl)pyrrolidine (Table 1, Entry 6) also failed to furnish any product at low temperature and caused decomposition of the starting material at higher temperature. We then explored the influence of additives and demonstrated that the reactions work well in the presence of chiral bis(oxazoline) as external chiral ligand (ECL) with a desired diastereoselectivity(13:87)(Table 1, Entry 7-8)[11].

Table 1 Optimizations of [2,3]-Wittig Rearrangement of precursor **6** [a]

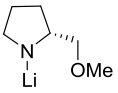




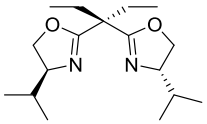
Base a: Lithium (*S*)-bis((*S*)-1-phenylethyl)amine



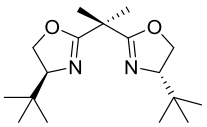
Base b:Lithium (*S*)-bis((*S*)-1-phenylpropyl)amine



Base c:Lithium (*R*)-2-(methoxymethyl)pyrrolidine



Ligand d: *(S,S)-Box-i-Pr*



Ligand e:*(S,S)*-Box-*t*-Bu

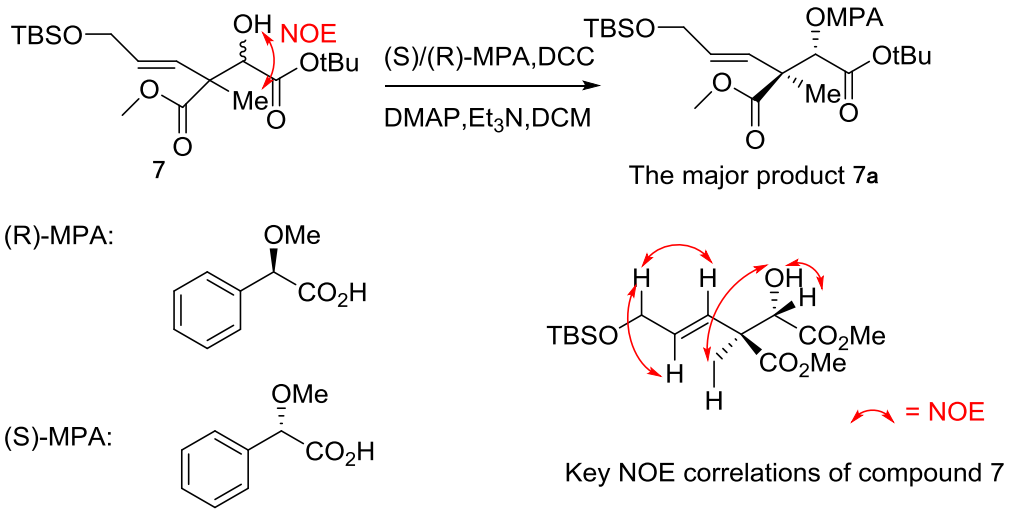
Entry	R	R_1	Base	additive	Yield[b]	*dr*[d]
1	Me	Me	LDA	HMPA	47.1%	27 : 73
2	Me	Me	NaHMDS	HMPA	NR[e]	/
3	Me	Me	TMPLi	HMPA	57.4%	25 : 75
4	Me	Me	Base a	HMPA	53.3%	43 : 56
5	Me	Me	Base b	HMPA	66.5%	32 : 67
6	Me	Me	Base c	HMPA	NR[e]	/
7	Me	Me	LDA	HMPA/Ligand d	48.1%	13 : 87
8	Me	Me	LDA	HMPA/Ligand e	51.2%	29 :71
9	tBu	Me	LDA	HMPA	53.6%	14 : 86
10	Ph	Me	LDA	HMPA	24.2%(undesire)	/
11	Tr	Me	LDA	HMPA	NR[e]	/
12	tBu	Et	LDA	HMPA	41.1%	16 : 84
13	tBu	tBu	LDA	HMPA	50.2%	14 : 86

[a](Reaction conditions, unless otherwise specified: 1mmol of precursor **6**, 2.2mmol LDA(lithium diisopropylamide), 1ml dry HMPA(Hexamethylphosphoramide) in 10ml THF at -78℃）.[b] (Isolated yields after purification by silica gel column chromatography.) [c] (The absolute configuration of products was determined by analyzing the ^{1}H NMR of its' *MPA* ester.) [d] (diastereoslective ratios (*dr*) were determined by ^{1}H NMR spectroscopy.) [e](NR=no reaction)

The presence of a large ester group on the allyloxy moiety was supposed to play some important role in producing high diastereoselectivity[7], so we next examined [2,3]-Wittig rearrangement of substrate with phenyl, tert-butyl and triphenyl

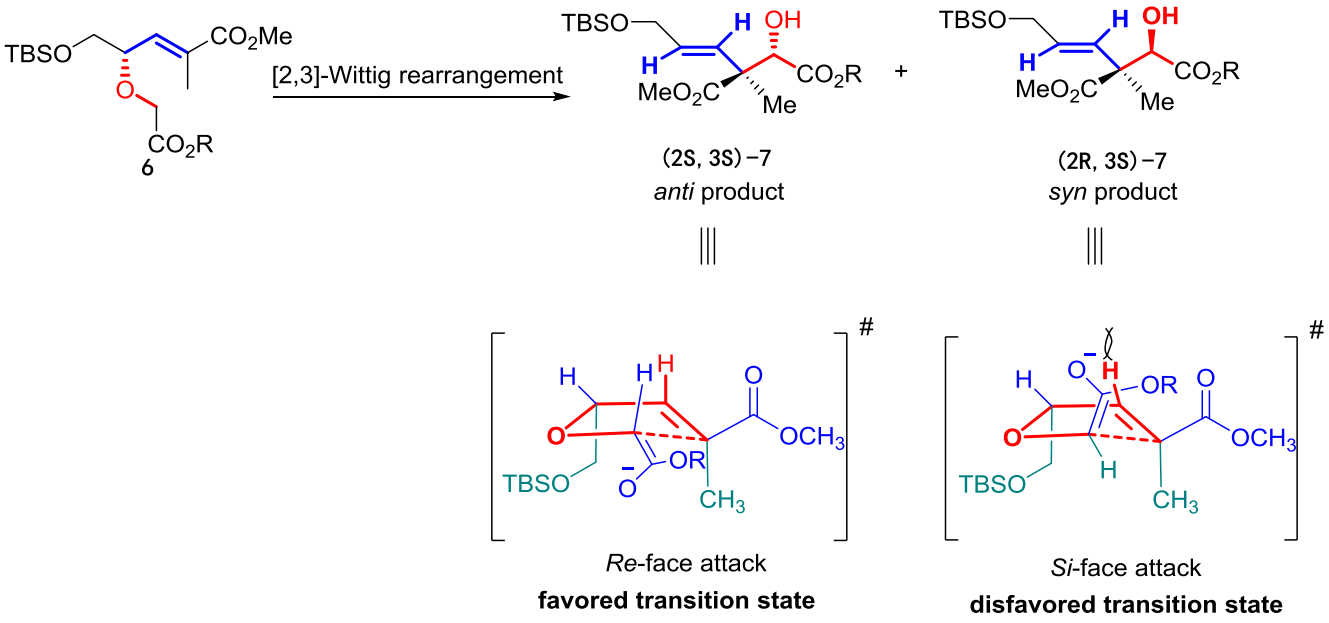
ester in the absence of chiral ligand (Table 1, Entry 9-11). To this end, 4-(2-tert-butoxyl-2-oxoethoxy)-enoate exhibit moderate yield and considerable *dr* value (14:86), compared with the reaction conducted in the presence of the stoichiometric external chiral ligand (3eq)[11]. We also test the influences of the unsaturated ester group on [2,3]-Wittig rearrangement that variations of unsaturated ester group (R_1=Et, t-Bu) had slightly decreased yield (Table 1, Entry 12-13) .

The absolute and relative configuration of **7** was confirmed by combined analysis of the NOESY spectra of **7** (R=*t*-Bu) and ^{1}H NMR spectra of (S)/(R)-*MPA* **7a**, a method reported by Ricardo Riguera et.al[12].



Scheme 4: The absolute and relative configuration of alcohol **7**

Although we have no definitive explanation at present for the unusual *threo* selection owing to the great complexities of this process, the observed sense of enantioselection (*2S*) might be interpreted as follows. The enolization leads to the metal-chelated (*E*)-enolate which undergoes the [2,3]-shift preferentially from the *Re*-face as depicted in Scheme 5, where the steric repulsion between the hydrogen and ester group would be minimized[13].

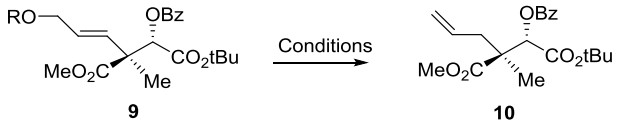


Scheme 5: The putative transition state of [2,3]-Wittig rearrangement

With the optimization of the [2,3]-Wittig rearrangement step, substrate **7** (R=*t*-Bu, R_1=Me)was chosen as the intermediate to be extended to Pantothenamides **1.** As outlined in Table **2**, we focus on the C-O cleavage and olefin migration of substrate

9 which was achieved by removal of TBS group of **7** and subsequent benzoylation of the resulting diol **8**. Following procedures adapted from Barrero's works (Table 2,Entry 1), we utilized Nugent's reagent ($Cp_2Ti(III)Cl$)[14] to induce the deoxygenation-reduction transformation at the first attempt, however, only about 20% corresponding olefin **10** was obtained, with 48% recovered starting material. Enlightened by a novel palladium-catalyzed formate reduction sequence[15], to our delight, the Palladium/P(n-Bu_3)-catalyzed debenzoylation and reduction of allylic benzoylate **9** produced the desired olefin **10** in good yield (68%), in sharp contrast to the corresponding PPh_3 as ligand (trace) (Table 2, Entry 2-3).

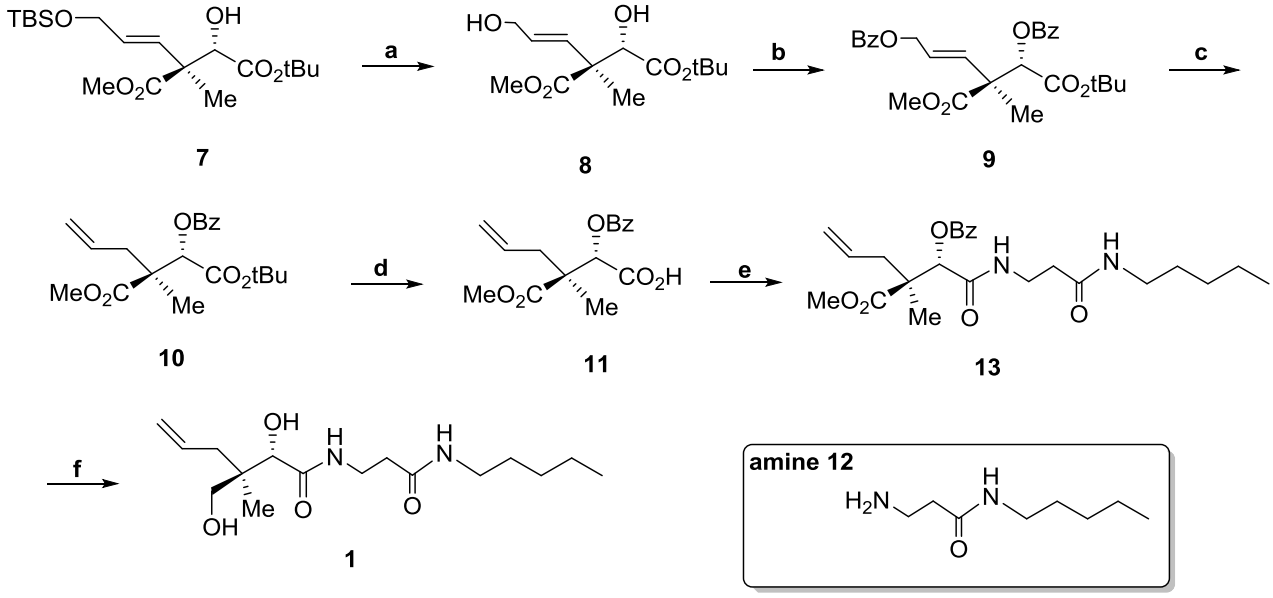
Table 2 The C-O Cleavage and Olefin Migration Sequence



9 **10**

Entry	R	Conditions	Yield
1	H	Cp_2TiCl_2/Mn/THF	20%
2	Bz	$Pd_2(dba)_3$/PPh_3/HCO_2NH_4,toluene, reflux	trace
3	Bz	$Pd_2(dba)_3$/P(n-Bu)$_3$/HCO_2NH_4,toluene, reflux	68%

Olefin **10** was then submitted deprotection to give the crude acid **11**(Scheme 3). Due to its instability , the crude acid **11**[3] was carried into coupling with deprotected amine **12** without further purification. Amine **12** was synthesized from Cbz-protected β-alanine and n-pentylamine according to literature procedure[16] and the ester reduction of amide **13** ultimately give the desired Pantothenamide **1** in moderate yield.



Reagents and Conditions: **a)** TBAF/THF, 4h, r.t. 86% **b**) BzCl, DMAP, Et_3N, DCM, r.t. 2h, 79% **c)** $Pd_2(dba)_3$, P(n-Bu)$_3$, HCO_2NH_4, toluene, reflux, 4h, 67%. **d)** TFA, DCM, overnight, r.t. **e**) EDCI, HOBt, amine **12**, DIPEA, THF,16h, two steps 41% **f**)$LiAlH_4$,THF,-15℃,45%.

Scheme 6: Synthesis of Pantothenamide **1**

3 Conclusions

We had conducted a new synthetic route that exploits the known alkyl methyl N-Pantothenamides derivative **1**, allowing for the installation of quaternary carbon moiety via [2,3]-Wittig rearrangement. The synthetic route feature two key elements, including [2,3]-Wittig rearrangement and palladium catalyzed formate reduction sequence. For the introduction of

the requisite quaternary carbon, [2,3]-Wittig rearrangement of ester **6** had been well studied for screening out the optimal condition. The above endeavors represent the diastereoselective synthetic route of allyl methyl N-Pantothenamide **1** and further investigation of enantiomeric rich [2,3]-Wittig rearrangement is underway in our laboratory, and these results will be reported in time.

4 Experimental section

General methods

^{1}H and ^{13}C NMR spectra were acquired on a Bruker AVANCE III-400 spectrometer with chemical shifts(δ) given in parts per million (ppm) relative to tetramethylsilane as the internal standard (δ=0.00 ppm). Purification by flash chromatography on silica gel(300-400 mesh) and ethyl acetate(EA)-petrol ether(PE) as eluents. Solvents were purified and dried by standard procedures prior to use. TLC was performed on silica gel GF_{254} plates and detected by charring with 5% ethanolic Phosphomolybdic acid hydrate or by placing under the UV(254nm,364nm) lamp.

General Procedure for [2,3]-Wittig Rearrangement

To a solution of LDA (or other metalated dialkylamides) (2eq, 2.57ml(2.0M), 5.14mmol) in THF (5ml) at -78℃was added a mixture of THF/HMPA solution (2.57ml/2.57ml) and additives (3eq) under Ar atmosphere. The reaction mixture was then stirred at this temperature for 30min and ester **6** (1g, 2.57mmol) in THF(2.5ml) was then injected into the reaction mixture while the color of solution turned into dark red. After the reaction was stirred at -78℃ for 4h, the reaction mixture was then pour into a cool saturated NH_4Cl and extracted with EtOAc (3×10ml). The combined extracts were washed with brine, dried over $MgSO_4$ and removed the solvent under reduced pressure. The residue was purified by chromatography on silica gel (Petroleum ether-EtOAc, 10:1) to afforded the product as light yellow oil or colorless oil.

Methyl (S,E)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylacrylate **(3)**

To a solution of (S)-Glyceraldehyde acetonide **2** (10g, 76.9mmol) in 100ml CH_2Cl_2 was added 27.8g(79.8mmol) methyl 2-(triphenyl-λ^{5}-phosphanylidene)propanoate at 0 ℃. The mixture was allowed to reach room temperature and stirred for 4h. The solvent was removed under reduced pressure and then added petrol ether (80ml) to removed triphenyl phosphorus oxide (Ph_3PO) by filtration. After evaporation of the solvent, The residue was purified by chromatography on silica gel (petroleum ether-EtOAc, 20:1) to afforded **3** (13.3g, 91%) as a colorless oil : Rf=0.53 (PE:EA)=10:1**.** IR(KBr) 2975, 1718, 1689 cm^{-1} [α]D28.8=+23.3(c,0.5,CH_3OH), ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (dd, *J* = 8.1, 1.4 Hz, 1H), 4.86 (dd, *J* = 14.2, 7.7 Hz, 1H), 4.16 (dd, *J* = 8.2, 6.3 Hz, 1H), 3.76 (s, 3H), 3.66 – 3.60 (t, *J*=7.6Hz, 1H), 1.90 (d, *J* = 1.3 Hz, 3H), 1.43 (d, *J* = 14.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.84, 138.54, 130.73, 109.85, 72.71, 68.73, 52.02, 26.61, 25.84, 13.01. HRMS(ESI-TOF) m/z[M+Na]$^{+}$ Calcd for $C_{10}H_{16}O_4$ 223.1049, Found 223.1125.

Methyl (S,E)-5-((tert-butyldimethylsilyl)oxy)-4-hydroxy-2-methylpent-2-enoate **(5)**

To a solution of **3** (1 g, 5.37 mmol) in mixed solvent (MeOH-H_2O:18ml/2.5ml) at ice bath was added 1ml conc.HCl. The mixture was stirred at this temperature for 2h. The reaction mixture was then added solid 1g $NaHCO_3$ to neutralization and evaporated the solvent under reduced pressure. The residue was extracted by EtOAc (3×10 ml) and the combined extracts were washed with water(10ml), brine(10ml), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to next step without further purification. Added TBSCl (1.16 g, 7.7 mmol) to a mixed solution of crude **4** and imidazol (1.61g,19.2mmol) in 20ml CH_2Cl_2 at 0 ℃. The mixture was then stirred at room temperature for 2h. The reaction mixture was quenched with methanol (0.3ml), diluted with DCM(30ml) and washed with 1N HCl (20ml) , saturated $NaHCO_3$ solution (20ml) ,brine(10ml) and dried over $MgSO_4$. The solvent was then removed under reduced pressure. The

residue was purified by chromatography on silica gel (petroleum ether-EtOAc,10:1) to afforded **5** (1.2g, 81%) as colorless oil : Rf= 0.24(PE:EA=10:1). IR(KBr) 3432, 1728, 1455cm^{-1} .[α]D28.8= -14(c,1,CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 8.1Hz,1.6 Hz, 1H), 4.42 (m, J=4.4Hz, 3.6Hz, 3.2Hz, 1H), 3.66 (s, 3H), 3.55 (dd, *J* = 10.1, 3.8 Hz, 1H), 3.44 – 3.38 (m, 1H), 2.57 (d, *J* = 3.3 Hz, 1H), 1.82 (d, *J* = 1.3 Hz, 3H), 0.82 (s, 9H), -0.00 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.06, 139.10, 130.31, 69.36, 65.68, 51.96, 25.85, 18.31, 13.13. HRMS(ESI-TOF) m/z[M+H]$^+$ Calcd for $C_{13}H_{26}O_4Si$ 275.1600,Found 275.1625.

Methyl(S,E)-4-(2-(tert-butoxy)-2-oxoethoxy)-5-((tert-butyldimethylsilyl)oxy)-2-methylpent-2-enoate **(6)** (R=*t*-Bu)

To a stirred solution of **5** (1g, 3.47mmol) and *tert*-butyl 2-bromoacetate (1.42g,7.3mmol) in dry DMF(16.5ml) at ice bath was added NaH (60%, 175.2mg) under Ar atmosphere. The stirred solution was allowed to room temperature for overnight. After the starting material was consumed, the mixture poured into a cool saturated NH_4Cl solution and extracted with EtOAc (3×10ml) . The organic phase washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by chromatography on silica gel (petroleum ether-EtOAc, 15:1) to afforded **6** (1.16g, 82%) as colorless oil .Rf=0.41(PE:EA=10:1). [α]D28.8= -4.3(c,1,CH_3OH). IR(KBr) 3422, 1768,1683, 1442 cm^{-1},^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 9.1Hz, 1.4Hz, 1H), 4.34 (m, *J*=9.4Hz, 1H), 3.98 (d, *J* = 16.2 Hz, 1H), 3.92 – 3.85 (d, *J* = 16.2 Hz, 1H), 3.79 (dd, *J* = 10.5, 5.8 Hz, 1H), 3.70 (s, 3H), 3.59 (dd, *J* = 10.5, 5.8 Hz, 1H), 1.85 (s, 3H), 1.41 (s, 10H), 0.82 (s, 9H), -0.00 (d, *J* = 3.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.33, 167.86, 138.68, 131.84, 81.55, 66.86, 65.36, 51.89, 28.06, 25.83, 18.30, 13.22. HRMS(ESI-TOF) m/z[M+H]$^+$ Calcd for $C_{19}H_{36}O_6Si$ 388.2281, Found 388.2256.

4-(tert-butyl) 1-methyl (2S,3S)-2-((E)-3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)-3-hydroxy-2- methylsuccinate (**7**)

The *tert*-butyl ester **6** was subjected to The General Procedure of [2,3]-Wittig rearrangement to afforded **7** as light yellow oil : Rf=0.35 (PE:EA=10:1). [α]D28.8= 28.3(c,1,CH_3OH). IR(KBr) 3425, 1772, 1490cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (d, *J* = 15.7 Hz, 1H), 5.91 – 5.79 (t, *J*=4.9Hz, 1H),4.36 (dd, *J* = 12.5, 5.6 Hz, 1H), 4.14 (m, 2H), 3.67 (s, 3H), 3.06 (t, *J* = 7.4 Hz, 1H), 1.40 (s, 11H), 1.29 (m, 2H), 1.20 (m, 1H), 0.84 (s, 9H), -0.00 (s, 6H). HRMS(ESI-TOF) m/z[M+Na]$^+$ Calcd for $C_{19}H_{36}O_6Si$ 411.2281, Found 411.2256.

4-(tert-butyl) 1-methyl (2S,3S)-3-(benzoyloxy)-2-((E)-3-(benzoyloxy)prop-1-en-1-yl)-2-methylsuccinate (**9**)

To a solution of alcohol **7**(100mg, 0.257mmol) in THF was added TBAF(74mg, 0.283mmol) at room temperature. After the reaction mixture was stirred for 4h, The solution was passed though a pot of silica gel and evaporated under reduced pressure to afforded light yellow oil which was directly subjected to next step. To a solution of crude diol in CH_2Cl_2(5ml) at ice bath was added triethyl amine(110mg, 10.9mmol), 4-Dimethylaminepyridine(5mg, 0.03mmol) and benzoyl chloride(112mg, 0.803mmol). The reaction mixture was stirred for overnight at room temperature. The mixture was then diluted with CH_2Cl_2 (10ml) and washed with 1N HCl (5ml), saturated $NaHCO_3$(5ml), brine(5ml) and dried over $MgSO_4$. After the evaporation of the solvent, the residue was purified by chromatography on silica gel (petroleum ether- EtOAc,20:1) to afforded **9** (85mg, two stpes： 68%) as colorless oil : Rf=0.56 (PE:EA=10:1) IR(KBr) 2958, 1772, 1689,1677,1455cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 5H), 7.43 (m, 7H), 6.14 (d, *J* = 15.8 Hz, 1H), 5.92 (m, 1H), 5.65 (s, 1H), 4.83 (dd, *J*=12.1Hz, 2H), 3.74 (s, 3H), 1.60 (s, 3H), 1.43 (d, *J* = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.28, 166.14, 134.05, 133.34, 132.95, 129.82, 129.77, 129.67, 129.59, 128.50, 128.44, 128.40, 128.31, 126.21, 126.10, 83.22, 75.41, 64.82, 52.55, 51.11, 27.89, 16.21. HRMS(ESI-TOF) m/z[M+H]$^+$ Calcd for $C_{27}H_{30}O_8$: 482.1941, Found 482.2047.

4-(tert-butyl) 1-methyl (2S,3S)-2-allyl-3-(benzoyloxy)-2-methylsuccinate (**10**)

Under Ar atmosphere, a mixture of $Pd_2(dba)_3$(5.7mg, 0.0062mmol), $P(nBu)_3$ (10mg, 0.05mmol)and HCO_2NH_4 (28.7mg, 0.455mmol) in toluene (5ml) was stirred for 10min at room temperature and **9**(100mg) in dry toluene (1ml) was then injected into the reaction mixture. The stirred mixture was allowed to reflux for 3-5h and then diluted with EtOAc (10ml). The organic phase was washed with water (10ml), brine(8ml), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was then purified by chromatography on silica gel (petroleum ether-EtOAc, 20:1) to afforded the desired product **10** (62mg, 68%) as colorless oil : Rf=0.63(PE:EA=10:1), IR(KBr) 2957, 1712, 1450cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.1Hz, 2H), 7.60 (t, *J*=7.4Hz, 1H), 7.47 (t, *J*=7.4Hz, 2H), 5.70 (m, 1H), 5.48 (s, 1H), 5.10 (dd, *J*=18.1Hz, *J*=8.3Hz, 2H), 3.71 (s, 3H), 2.46 (m, 2H), 1.44 (s, 9H), 1.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.33, 166.69, 165.62, 133.36, 132.90, 132.57, 129.79, 128.50, 119.13, 83.04, 76.05, 52.07, 51.94, 49.24, 48.95, 41.22, 39.79, 27.98, 27.86, 18.12, 16.38. HRMS(ESI-TOF) m/z[M+H]$^+$ Calcd for $C_{20}H_{26}O_6$: 363.1729, Found 363.1697.

(2S,3S)-3-(methoxycarbonyl)-3-methyl-1-oxo-1-((3-oxo-3-(pentylamino)propyl)amino) hex-5-en-2-yl benzoate. (**13**)

Allylic **10**(100mg, 0.276mmol) in 1ml CH_2Cl_2 was added into 20%TFA/CH_2Cl_2 (v/v, 5ml) solution and stirred at room temperature for overnight. The solvent was evaporated under reduced pressure to obtained a yellow oil which subjected to next step without further purification. In a separated three necked, round-bottomed flask, EDCI(190mg, 0.99mmol) and HOBt(89.4mg, 0.66mmol) was added in 10ml THF while the crude acid was dissolved in 2ml THF and then added into the reaction mixture. The amine **12** in 1ml THF and DIPEA(214mg, 1.65mmol) was subsequently added the solution. The reaction was stirred at room temperature for overnight and diluted with 10mlCH_2Cl_2 and then washed with 1N HCl(5ml), saturated $NaHCO_3$ solution(5ml) and brine, dried over $MgSO_4$. After evaporation of solvent, the residue was purified by chromatography on silica gel (petroleum ether:EtOAc=1:1) to afforded the desired product **13** (49mg, 41%) as colorless oil: Rf=0.45(PE:EA=2:3) IR(KBr) 3446, 1789, 1658, 1457 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.5 Hz, 2H), 7.63 (t,*J*=7.4Hz, 1H), 7.50 (t, *J*= 7.8Hz, 2H), 6.94 (t, J=5.7Hz, 1H), 5.80 (s, 1H), 5.68 (m , 2H), 5.04 (t, *J*=8.2Hz, 2H), 3.77 (s, 3H), 3.52 (m, 2H), 3.16 (m, 2H), 2.57 (dd, *J* = 13.5 Hz, *J*=7.4Hz, 1H), 2.33 (m, 3H), 1.45 (m, 3H), 1.30 (m, 9H), 0.89 (t, J= 7.1Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.77, 171.04, 168.00, 165.21, 133.85, 132.45, 129.93, 129.89, 128.82, 128.74, 128.69, 119.08, 52.21, 49.81, 41.12, 39.57, 35.56, 35.49, 29.67, 28.94, 24.43, 23.95, 22.30, 16.62, 13.95. HRMS(ESI-TOF) m/z[M+H]$^+$ Calcd for $C_{24}H_{34}N_2O_6$: 447.2417, Found 447.2443.

(2S,3R)-N-(3-(butylamino)-3-oxopropyl)-2-hydroxy-3-(hydroxymethyl)-3-methylhex-5-enamide **1**

To a solution of ester **13 (** 50mg, 0.112mmol) in THF at -15℃ was added $LiAlH_4$ (18mg, 0.45mmol) under Ar atmosphere. The mixture stirred at this temperature for 4 hours, and then added 1ml saturated Na_2SO_4 ,10ml EtOAc into this mixture . The solution was passed though a pot of celatom and the organic phase was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by chromatography(petroleum ether:EtOAc=1:2) on silica gel to afforded the desired **1** (17mg, 45%) as colorless oil. Rf=0.14(PE:EA=1:2). IR(KBr) 3459, 1766, 1623, 1453 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (m, 2H), 5.13 (d, *J*=5.4Hz ,1H), 5.09 (s, 1H), 4.35 (s, 1H), 3.71 (m, 2H), 3.13 (q , *J*=6.9Hz, 2H), 2.44 (t, *J*=7.1Hz, 3H), 2.36 – 2.27 (m, J=7.1Hz, 1H), 1.41 (s, 2H), 1.23 (m, 6H), 1.16 (s, 3H), 0.82 (t, *J*=6.8Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 178.84, 176.31, 131.22, 119.16, 75.69, 71.10, 47.51, 38.92, 38.68, 34.05, 32.82, 28.68, 28.11, 28.01, 21.30, 17.41, 12.94. HRMS(ESI-TOF) m/z[M+H]$^+$ Calcd for $C_{24}H_{34}N_2O_6$: 301.2049, Found 301.2122.

Supporting Information [The ^{1}H NMR and ^{13}C NMR spectrum of compound **1~13,** and the NOESY spectra of compound **7**(R=Me)]. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

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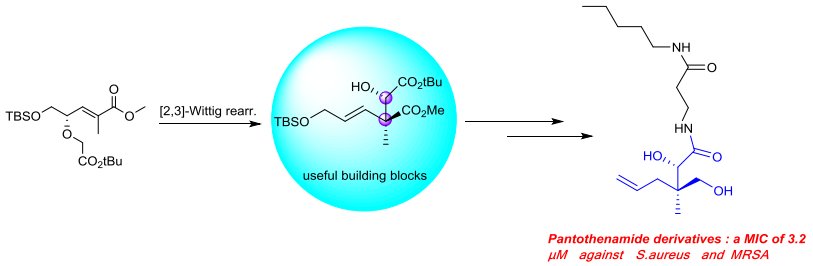
图文摘要

A synthetic route to access allyl-methyl-N-Pantothenamide *via* [2,3]-Wittig rearrangement



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Allyl-methyl-N-Pantothenamide was antimicrobial with unique quaternary carbon and vicinal secondary alcohol moiety which was constructed by asymmetric [2,3]-Wittig rearrangement. The homoallylic alcohol products , originated from [2,3]-Wittig variant of trisubstituted allylic ether, was a useful building blocks which could straightforwardly furnished the Pantothenamide derivatives with *MIC* of 3.2μM against *S.aureus* and *MRSA*.

