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Stereoselective Formal Synthesis of (-)-mesembrane *via* Asymmetric Allylation and Resoluting Condensation Reactions†

Jihye Park, Young Kwang Kim, and Guncheol Kim*

Department of Chemistry, College of Natural Science, Chungnam National University, Daejon 305-764, Korea
**E-mail: guncheol@cnu.ac.kr*
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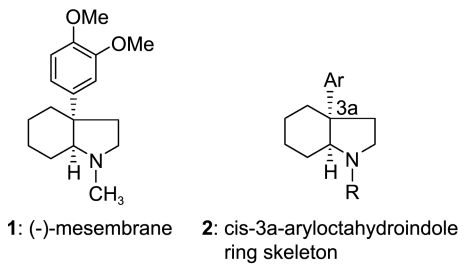
The enantioselective synthesis of quaternary carbon stereocenters and application to natural products has been a formidable challenge to synthetic organic chemists.[1] Ways to quaternary stereocenters are demanded very much given the prevalence of the centers in various attractive natural products. One of the most promising methods for the purpose is the Pd-catalyzed alkylation of prochiral stabilized enolates.[2] Although these methods have been useful, regioselectivity can be meet only in the case of single acidic site or a large p*K*a difference between two acidic sites to prevent the mixture formation. Instead, Tsuji allylation pathway from allyl enol carbonates which would be formed regioselectively by controlled methods prevented the production of mixtures of allylated products and allowed the neutral reaction conditions to yield good to excellent selectivity.[3]

Recently, we published the stereoselective synthesis of (-)-mesembrane **1** which contains a quarternary center.[4] Mesembrane **1** is a well known member of the *Sceletium* alkaloids,[5] which has the basic structural element of *cis*-3a-aryloctahydroindole skeleton **2** (Figure 1). In the previous synthesis, we have applied desymmetrization of 1,3-dicarbonyl groups of cyclohexadione by intramolecular condensation with chiral amides. The maximum selectivity was moderately 3:1. So, we wanted to find out the strategy which would afford enhanced selectivity, and decided to combine Tsuji asymmetric allylation and the resoluting condensation step using a proper chiral auxilary. In the condensation step, it is anticipated that the energy difference of the diastereomeric aminol intermediates formed from attack of chiral amide to carbonyl group presumably would cause the difference of formation rates and the final production yields. We should find out the matching chiral auxiliary which would result in optimum resolution in the cyclization process to afford the desired isomer with better selectivity (Scheme 1).

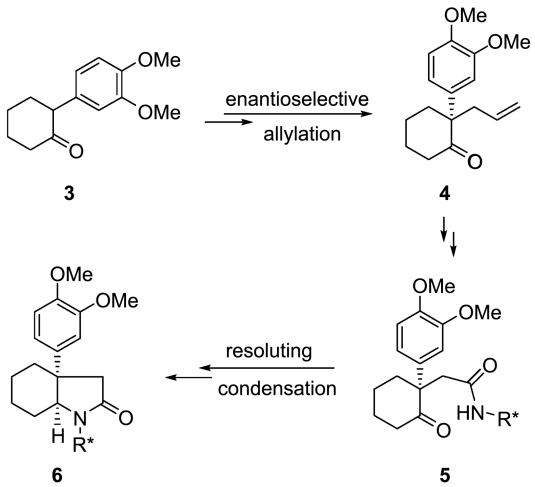


1: (-)-mesembrane **2**: cis-3a-aryloctahydroindole ring skeleton

Figure 1

First, in the condensation reaction of chiral amide and carbonyl group of **7**, we wanted to see how much resoluting selectivity would be generated through diastereomeric aminol intermediate (Table 1). The inseparable amide ketone diastereomers **7** could be prepared by employing the known procedure from **3**.[4] Cyclization has been found to proceed best in toluene at 65 °C in the presence of TsOH. Among four chiral auxiliaries selected for the preparation of **7**, two (Entry 1 and 2) provided 2:1 selectivity in 50 and 70% yields. Although the selectivity was moderate, we expected that this step would be helpful to increase the selectivity as an ancillary step and provide a known chiral intermediate.

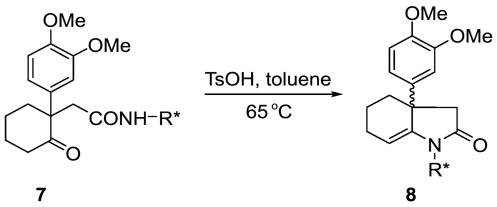
We have tried asymmetric allylation of allyl enol carbonate **9** to find out the optimum condition including the best chiral ligand. The required intermediate **9** was prepared from **3** by the reaction with allyl chloroformate in 67% yield as a single isomer. Various reaction conditions have been adopted in the allylation reaction using several known chiral ligands.[6] And we found that (*R*,*R*)-ANDEN-phenyl Trost ligand **11** (5.5 mol %) afforded the best selectivity 83:17 in 58% yield in toluene at −78 °C in the presence of $Pd_2(dba)_3$ (2.5 mol %). The isomeric ratio was determined by chiral HPLC column chromatography (Scheme 2). At this stage the absolute configuration of the quarternary center could not be determined,



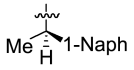
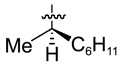
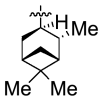
Scheme 1

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.

Table 1. Study of cyclization of **7**



7 **8**

Entry	R	Yied (%)	Ratio[a]
1		50	2:1
2		70	2:1
3		74	1:1
4		69	1:1

[a]The ratio was determined by 1H-NMR

therefore, we decided to compare the corresponding cyclized isomer obtained from the major isomer of **10** with the known chiral intermediate.

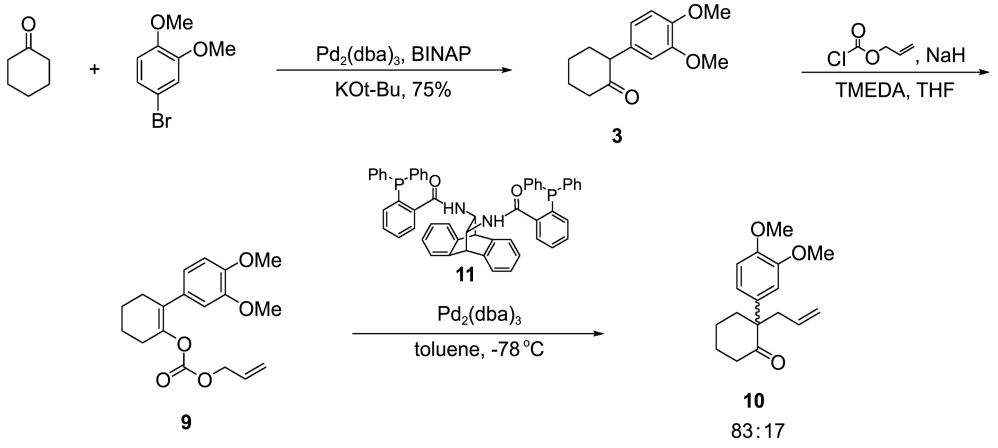
The enantiomeric mixture **10** was converted to the diasteromeric mixture of amide **12** through dihydroxylation followed by oxidative cleavage to carboxylic acid, and amide formation with (*R*)-1-(1-naphthyl)ethylamine provided compound **12** in 63% yield in two steps. The ratio of mixture **12** remained same 83:17. The acidic condition used in Table 1 allowed the cyclization of **12** to **13** in 62% with an enhanced ratio of 9:1. When the antipode mixture of **12** having (*S*)-1-(1-naphthyl)ethylamine as an chiral auxiliary in the amide was subjected to cyclize, similar selectivity was detected, however, only in the case of less than 10% yield production. For the reconfirmation of the structure of **13**, compound **13** was reduced by the known reaction condition, Et_3SiH in trifluoroacetic acid to afford the separable compounds **14** and **15** with the same 9:1 ratio in 71% yield, allowing the formal synthesis of (-)-mesembrane. The spectra of **14** were identical to those known.[7]

In summary, we have shown a more selective way to (-)-mesembrane by applying the combination of enantioselective allylation and resoluting chiral amide-ketone cyclization. The chiral ligand (*R,R*)-ANDEN-phenyl Trost ligand **11** for the enantioselective allylation and (*R*)-1-(1-naphthyl)ethylamine auxiliary of **12** for the cyclization matched to give the enhanced selectivity in the synthesis of **14**.

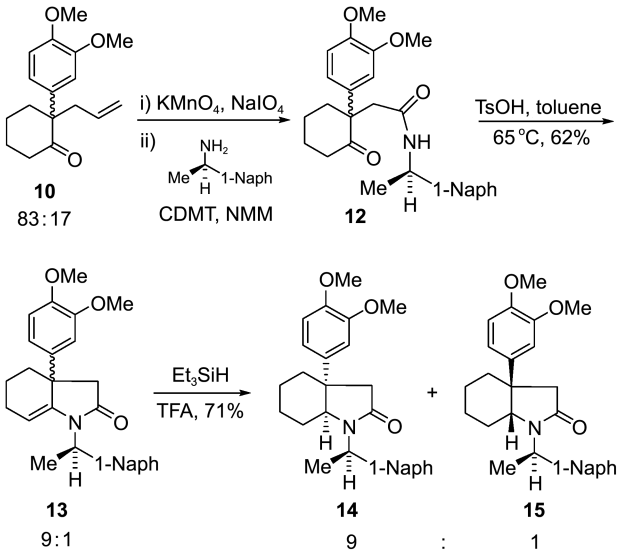
Experimental Section

2-(3,4-Dimethoxyphenyl)cyclohexanone (3). To a solution of cyclohexanone (294 mg, 3.0 mmol), potassium *tert*-butoxide (146 mg, 1.3 mmol), $Pd_2(dba)_3$ (27.5 mg, 3.0%) and (2-biphenyl) di-*tert*-butylphosphine (44.8 mg, 7.2%) in anhydrous toluene (2 mL), was added 4-bromoveratrole (217 mg, 1.0 mmol) sequentially. The solution was heated in an oil bath at 80 °C for 20 h. The reaction was quenched with aqueous 1M HCl and extracted with 20 mL of ethylacetate. The organic layer was wahed with water and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was separated by silica gel column chromatography (ethylacetate : hexane = 1 : 5) to yield 175 mg of product **3** (75%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.84 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 6.66 (s, 1H), 3.86 (s, 6H), 2.5 (m, 2H), 2.19 (m, 2H), 2.02 (m, 2H), 1.82 (m, 2H).

Allyl 2-(3,4-dimethoxyphenyl)cyclohex-1-enyl carbonate (9). To a suspension of **3** (234 mg, 1.0 mmol) in distilled THF(5 mL) was added TMEDA(349 mg, 3.0 mmol) and 55% NaH (96.0 mg, 4.0 mmol) at room temperature. The reaction mixture was heated to reflux for 1 h. After the resulting solution was cooled by ice-water bath for 5 min, allyl chlorofamate (0.213 mg, 2.0 mmol) was injected to the solution at 0. After stirring for 1 h, saturated aqueous ammonium chloride was poured into the reaction flask. The mixture was extracted with diethyl ether (3 × 10 mL). The organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (ethylacetate : hexane = 1 : 5) to yield 213 mg of **9** (67%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.84 (s, 1H), 6.81 (s, 2H),



Scheme 2



Scheme 3

5.81 (m, 1H), 5.24 (m, 2H), 4.52 (dd, J = 5.6, 1.2 Hz, 2H), 3.85 (d, J = 8.0 Hz, 6H), 2.40 (br, 2H), 2.32 (br, 2H), 1.83(d, J = 4.8 Hz, 2H), 1.76 (d, J = 5.6 Hz, 2H).

2-Allyl-2-(3,4-dimethoxyphenyl)cyclohexanone (10). To a dried round-bottom flask was added with allyl 2-(3,4-dimethoxyphenyl)cyclohex-1-enyl carbonate (318 mg, 1.0 mmol), $Pd_2(DBA)_3$ (22.9 mg, 2.5%), (*R,R*)-ANDEN-phenyl Trost ligand (44.8 mg, 5.5%) dried under vacuum, and then backfilled with nitrogen. To this round-bottom flask charged with nitrogen was injected toluene (10 mL), and the solution was stirred at −78 °C for 24 h. The reaction mixture was filtered, and concentrated under reduced pressure, and the crude product was purified by by silica gel column chromatography (ethylacetate : hexane = 1 : 6) to yield 159 mg of the enantiomeric mixture of **10** (58%, 83:17); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.84 (d, J = 8.0 Hz, 1H), 6.72 (dd, J = 8.4, 2.4 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 5.44 (m, 1H), 4.91 (t, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 2.62-2.49 (m, 2H), 2.44-2.26 (m, 3H), 1.95 (m, 1H), 1.84-1.68 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 213.5, 149.5, 148.1, 134.6, 133.1, 119.3, 117.7, 111.5, 110.4, 56.4, 56.1, 45.1, 40.1, 34.9, 28.1, 21.6; EIMS 274 (M^+).

***(R)*-2-(1-(3,4-Dimethoxyphenyl)-2-oxocyclohexyl)-N-(1-(naphthalen-2-yl)ethyl)acetamide (12).** To a suspension of $NaIO_4$ (1.28 g, 6.0 mmol) in 7 mL H_2O was added to a solution of 2-allyl-2-(3,4-dimethoxyphenyl)cyclohexanone mixture **10** (274 mg, 1.0 mmol) in 5 mL acetone. The reaction solution was stirred for 5 min and a solution of $KMnO_4$ (31.6 mg, 0.2 mmol) in 2 mL H_2O was added. After 16 h, the reaction mixture was filtered, acidified, and extracted with ethylacetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residues of concentration was purified by column chromatography (ethylacetate : hexane = 1 : 1) to yield 202 mg of the corresponding acid (69%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.84 (d, J = 8.4 Hz, 1H), 6.77 (dd, J = 8.4, 2.0 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.80 (d, J = 15.6 Hz, 2H), 2.66 (d, J = 15.6 Hz, 1H), 2.36 (m, 2H), 2.17 (m, 1H), 1.95 (m, 1H), 1.76 (m, 3H). To a solution of the acid obtained (292 mg, 1.0 mmol) in acetonitrile (4 mL) was added *N*-methyl morpholine (152 mg, 1.5 mmol), CDMT (263 mg, 1.5 mmol). After stirring for 5 min, (*R*)-(1)-(1-naphthyl)ethylamine (188 mg, 1.1 mmol) was added. The reaction mixture was stirred for 2 h. The solvent was removed under reduced pressured and the crude product was purified by column chromatography (ethylacetate:hexane = 1 : 2) to afford 388 mg of mixture **12** (90%). The major portion of **12** : ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.53-7.35 (m, 4H), 6.84 (d, J = 8.4 Hz, 1H), 6.70 (dd, J = 8.4, 2.4 Hz, 1H), 6.66 (d, J = 2 Hz, 1H), 5.80 (q, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 2.87 (dd, J = 14.8, 2.4 Hz, 1H), 2.76 (d, J = 13.6 Hz, 1H), 2.40 (d, J = 13.6 Hz, 1H), 2.32 (dd, J = 13.6, 6.0 Hz 1H), 2.20 (d, J = 13.6 Hz, 3H), 1.86-1.63 (m, 5H), 1.44 (d, J = 6.8 Hz, 3H), 1.33 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 214.0, 169.4, 149.6, 148.4, 138.9, 134.0, 132.6, 131.0, 128.9, 128.2, 126.4, 125.9, 125.3, 123.7, 122.5, 119.1, 111.6, 109.6, 56.4, 56.0, 47.8, 44.4, 39.8, 34.8, 27.7, 21.4, 21.0.

Compound (13). A solution of **12** (44.5 mg, 0.1 mmol) and TsOH (20.9 mg, 0.11 mmol) in toluene (5 mL) was heated at 65 °C for overnight. The solvent was removed under reduced pressured. The residue of concentration was purified by column chromatography (ethylacetate : hexane = 1 : 2) to yield was 27.8 mg of 9 : 1 mixture of **13** (62%). The major portion of **13**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.56-7.45 (m, 4H), 6.87 (dd, J = 8.0, 2.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 6.20 (d, J = 7.2 Hz, 1H), 4.91 (t, J = 3.6 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 2.87 (d, J = 16 Hz, 1H), 2.64 (d, J = 16 Hz, 1H), 2.08-1.95 (m, 3H), 1.89 (d, J = 7.2 Hz, 4H), 1.67-1.59 (m, 3H), 1.41-1.36 (m, 1H), 1.12-1.10 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.4, 148.8, 147.9, 141.6, 136.9, 134.0, 132.2, 129.0, 128.5, 126.8, 126.0, 125.1, 124.7, 124.4, 123.9, 119.9, 110.9, 109.9, 104.4, 56.0, 55.7, 55.4, 47.0, 45.1, 36.4, 23.0, 17.5 ; EIMS 427 (M^+).

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