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SYNTHESIS OF 1-AZASPIRO[4.5]-7-DECEN-2-ONE FROM L-ASPARAGINE AND L-ASPARTIC ACID

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Dedicated to Professor Somsak Ruchirawat on occasion of his 80th birthday

Abstract – A synthetic strategy for 1-azaspiro[4.5]-7-decen-2-one based on *N*-acyliminium spirocyclization is reported. The common core structure found in biologically active alkaloids such as FR901483, TAN1251 and lepadiformine was synthesized via chiral *N*-alkyl-3-dibenzylaminosuccinimide intermediates. The chiral succinimides were synthesized in 2 steps from L-aspartic acid or 3 steps from L-asparagine.

INTRODUCTION

Spiro[cyclohexane-pyrrolidine] is a common core structure found in various biologically active alkaloids such as FR901483, TAN1251 and lepadiformines. These alkaloids possess 1-azaspiro[4.5]decane core as part of more complex structural architectures. FR901483 is an immunosuppressant isolated from the fermentation broth of *Cladobotryum* sp. No. 11231 while TAN1251 is a muscarinic acetylcholine receptor from a culture of *Penicillium thomii* RA-89.[1,2] Lepadiformines are tricyclic pyrrolo[2,1-*j*]quinoline alkaloids from the tunicate *Clavelina lepadiformis* and *Clavelina moluccensis* with various biological activities such as cytotoxicity against nasopharynx carcinoma and non-small-cell lung carcinoma as well as cardiovascular effect.[3] These compounds could be isolated in only minute amounts from the natural sources; therefore, synthetic means are necessary to provide sufficient quantities for further medicinal study and development. In addition to natural products, synthetic non-natural analogs have found medicinal applications due to improved efficiency and optimized undesired side effects such as toxicity. In this regard, D-ring homologs of cytotoxic cephalotaxine from *Cephalotaxus* sp. have been synthesized and they contain the spiro[cyclohexene-pyrrolidine] core (Figure 1).[4-6]

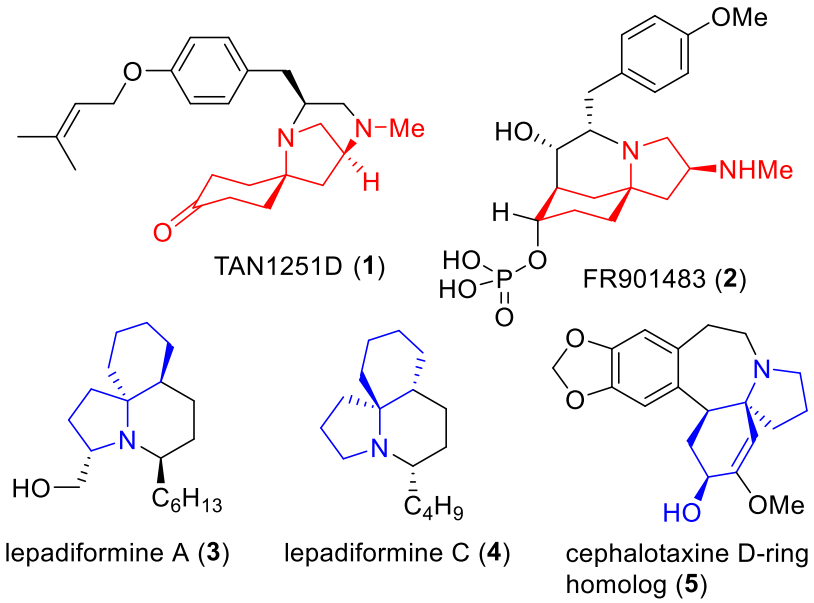
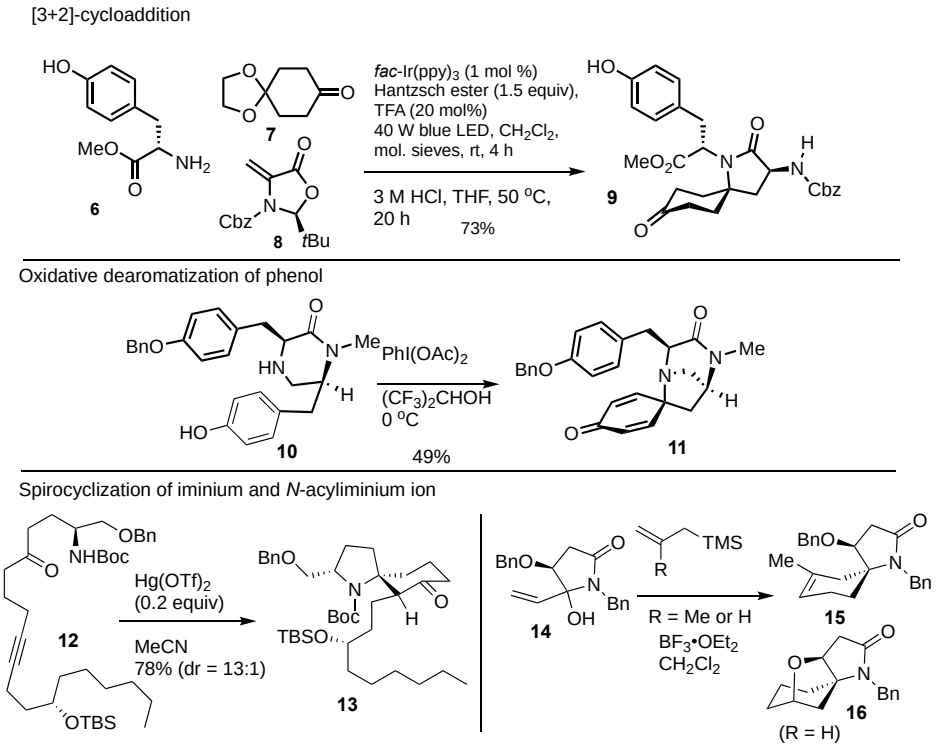


Figure 1. Alkaloids with spiro[cyclohexane-pyrrolidine] core

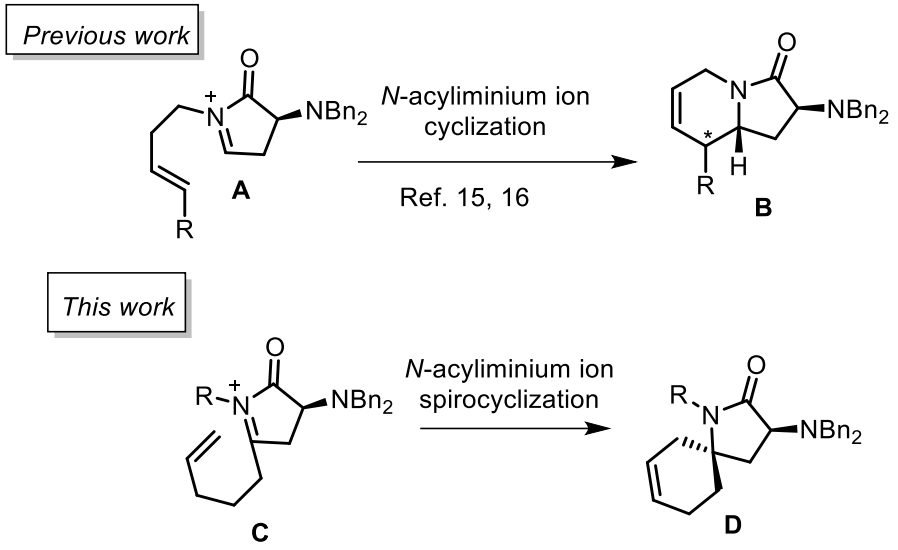
There have been several reported syntheses of spiro[cyclohexene-pyrrolidine] alkaloids. Some selected examples are discussed here focusing on the construction of the core structure of the target molecules (Scheme 1). Straightforward chemistry was used by Fukuyama in 2004 for a racemic synthesis of FR901483 in which a triple Michael reaction of nitromethane and methyl acrylate was followed by nitro group reduction and lactam formation to make the spiro[cyclohexane-pyrrolidone] core of the molecule.[7] Several asymmetric syntheses using chiral pool starting materials have been reported. These syntheses differed in the key transformation that constructed the spirocyclic center. In 2000, Snider used a cyclohexanone derivative as the starting material which reacted with tyrosine-derived hydroxylamine to form chiral imine oxide. Subsequent [3+2] dipolar cycloaddition with ethyl acrylate gave isooxazoline and hydrogenolysis followed by lactam formation yielded spiro[cyclohexane-pyrrolidone] core of TAN1251C.[8] A similar approach was applied by Gaunt and coworkers in 2020 for enantioselective synthesis of (-)-FR901483 and (+)-TAN1251C from a common key intermediate. Condensation of L-tyrosine methyl ester **6** with 1,4-cyclohexanedione monoethylene acetal **7** and subsequent reaction with a dehydroalanine derivative **8** in a photocatalytic olefin hydroaminoalkylation in the presence of Hantzsch ester gave the key intermediate spiro[cyclohexanone-pyrrolidone] **9**.[9] Oxidative dearomatization was used in syntheses of TAN1251D by Wardrop in 2001 and Honda in 2002. Honda reported a synthesis of TAN1251D using intramolecular oxidative spirocyclization of phenol and piperazine moieties in compound **10** to form spiro[piperazine-cyclohexanone] **11** as the key reaction while Wardrop started the synthesis with more readily available *O*-methyltyrosine derivative.[10,11] Spirocyclizations of *in-situ* generated iminium or *N*-acyliminium ion have also been employed in spirocyclic alkaloid syntheses. In 2002 Kibayashi reported a

synthesis of lepadiformine A featuring spirocyclization of amino-ketone-diene to form 1-azaspiro[4.5]decane core in a single step.[12] In a similar fashion, in 2015, Morimoto reported a synthesis of lepadiformine A featuring mercury triflate mediated spirocyclization of amino-ketone-alkyne **12** to yield spiro[cyclohexanone-pyrrolidine] **13**.[13] In 2020 Pyne reported tandem conjugate addition/*N*-acyliminium spirocyclization of benzyloxy-hydroxylactam **14** to give spirocyclohexene-pyrrolidone **15** or 1-benzyl-hexahydro-5,8a-methanooxepino[3,2-*b*]pyrrol-2(1*H*)-one **16**.[14] Herein we report a synthetic procedure for 1-azaspiro[4.5]-7-decen-2-one based on *N*-acyliminium spirocyclization.



Scheme 1. Selected examples of previously reported synthesis of spiro[cyclohexane-pyrrolidone]

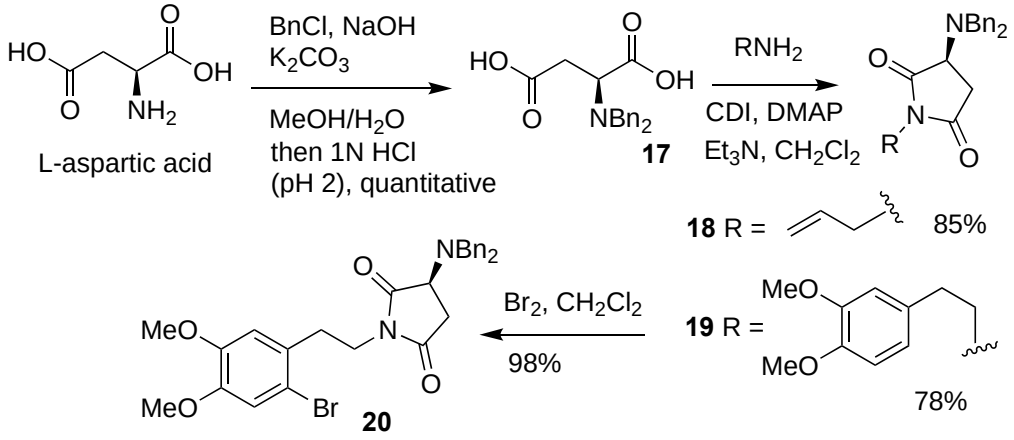
In our previous work[15,16] we employed cyclization of chiral *N*-acylpyrrolidinium ion synthesized from L-aspartic acid or L-asparagine. The 2-arylethyl or 3-alken-1-yl on the nitrogen atom reacted as nucleophile in the cyclization to give indolizidinone product. The dibenzylamino group gave the reaction stereocontrol and the product was obtained with high diastereoselectivity. In this work, we hypothesize that when the *N*-substituent of the pyrrolidinium ion cannot act as the nucleophile, the γ-4-penten-1-yl substituent of the pyrrolidinium ion can cyclize onto the γ-carbon to give the spiro[cyclohexene-(3-dibenzylaminopyrrolidin-2-one)] product. This structural moiety is suitable for synthesis of various 1-azaspiro[4.5]decane alkaloids, especially FR901483 and TAN1251D with the amino group at C3 (Scheme 2).



Scheme 2. *N*-Acyliminium ion cyclization vs *N*-acyliminium spirocyclization

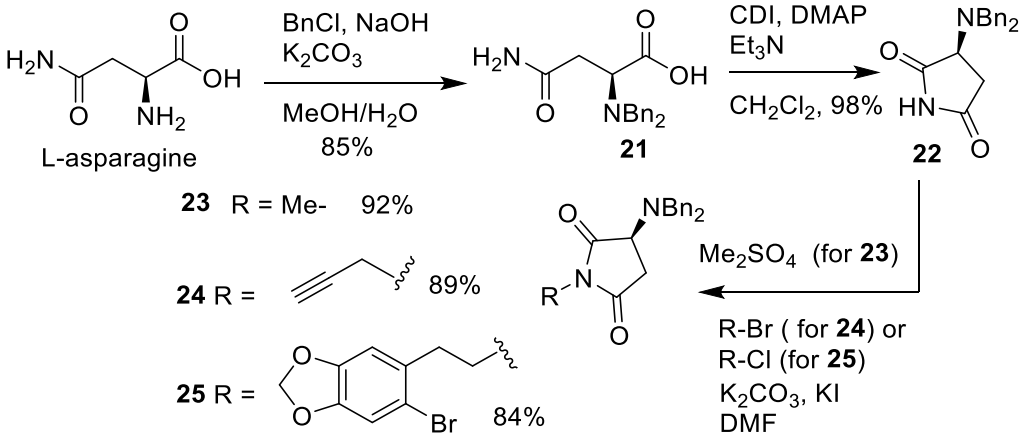
RESULTS AND DISCUSSION

The key chiral succinimide intermediates were synthesized in two routes depending on the availability of the starting materials. In the first route, the key intermediate was synthesized from the amino acid in 2 steps from L-aspartic acid (Scheme 3). L-Aspartic acid underwent *N*-benzylation to give dibenzylaspartic acid **17** with benzyl chloride in basic conditions. Careful adjustment of the pH of the reaction mixture resulted in quantitative formation of *N*,*N*-dibenzylaspartic acid **17** as white precipitates. Succinimide formation by reaction of *N*,*N*-dibenzylaspartic acid with allylamine or homoveratrylamine in the presence of carbonyldiimidazole (CDI) and triethylamine gave *N*-allyl-3-dibenzylaminosuccinimide **18** and *N*-[2-(3,4-dimethoxyphenyl)ethyl-3-dibenzylaminosuccinimide **19**, respectively, in good yields. Bromination of the dimethoxyphenyl moiety of **19** with 2% bromine solution in dichloromethane yielded *N*-[2-(bromoarylethyl)]succinimide **20**.



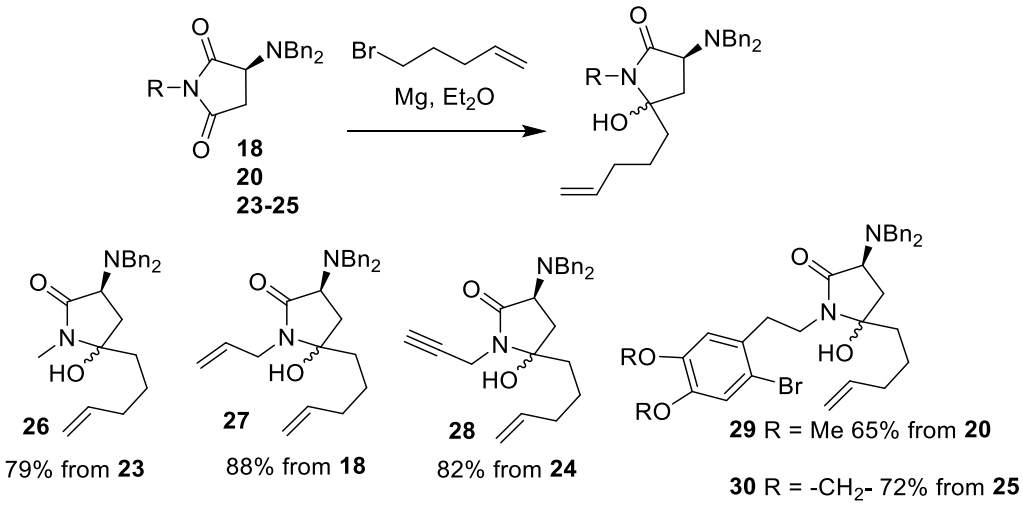
Scheme 3. Preparation of *N*-alkyl-3-dibenzylaminosuccinimides from L-aspartic acid

In the second route, the chiral succinimides were synthesized in 3 steps from L-asparagine (Scheme 4). Benzylation of L-asparagine with benzyl chloride in basic condition gave *N*,*N*-dibenzylasparagine **21** in good yield. Treatment of this compound with CDI resulted in succinimide formation to give 3-dibenzylaminosuccinimide **22** in excellent yield. *N*-Methylation of the succinimide was accomplished using dimethyl sulfate as alkylating agent to give *N*-methylsuccinimide **23**. Propargyl bromide as alkylating agent in the presence of potassium carbonate and catalytic potassium iodide in DMF gave *N*-propargylsuccinimide **24**. *N*-Alkylation with 6-bromohomopiperonyl chloride in the same condition gave *N*-(2-bromoarylethyl)succinimide **25** in a straightforward fashion.



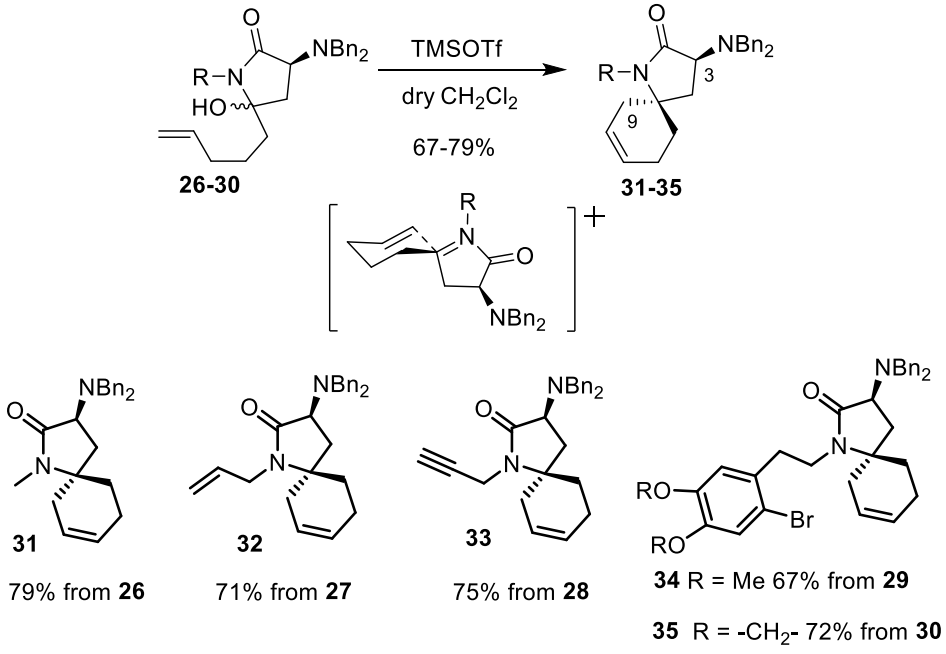
Scheme 4. Preparation of *N*-alkyl-3-dibenzylaminosuccinimides from L-asparagine

Reaction of the succinimide with *in-situ* generated 4-pentenylmagnesium bromide was accomplished by addition of a solution of *N*-alkyl-3-dibenzylaminosuccinimide to the reaction mixture containing 5-bromo-1-pentene and magnesium in diethyl ether (Scheme 5). The resulting mixture contained regioisomeric 3-dibenzylamino-γ-pentenyl-γ-hydroxylactam as the major product along with small amount of 4-dibenzylamino-γ-pentenyl-γ-hydroxylactam (ca. 6:1 ratio).[17] The major product was obtained from addition of the Grignard reagent to the less hindered carbonyl group of the succinimide. Although the regioisomers could be chromatographically separated, the crude reaction mixture could be carried out to the next step in which only 3-dibenzylamino-γ-pentenyl-γ-hydroxylactam gave the desired cyclized product and the minor regioisomer underwent dehydration and the resulting products were more easily separable.



Scheme 5. Synthesis of γ-pentenyl-γ-hydroxylactams from *N*-arylethyl-3-dibenzylaminosuccinimides

N-Acyliminium spirocyclization of the γ-pentenyl-γ-hydroxylactams upon treatment with TMSOTf gave 1-azaspiro[4.5]-7-decen-2-ones as single diastereomer in good yields. Relative configuration of the product was determined by NOESY experiments in which correlation between H3 and a H9 allylic proton was observed (Scheme 6). The stereochemical outcome can be accounted for by addition of the alkene to the *N*-acyliminium ion from the opposite side of the dibenzylamino group. The functionality of the *N*-alkyl groups was compatible with the reaction conditions. *N*-Allyl and alkyne did not participate during the reaction. In addition, 2-bromo-4,5-dimethoxyphenylethyl and 5-bromobenzo[*d*][1,3]dioxol-6-yl did not cyclize in a Pictet-Spengler reaction to form benzoindolizidines.



Scheme 6. *N*-Acyliminium spirocyclization

In conclusion, we have synthesized five *N*-alkyl-1-azaspiro[4.5]-7-decen-2-ones with different *N*-alkyl substituents as shown in Scheme 6. The *N*-substituent of the pyrrolidone ring can be selected to fit the synthesis of respective alkaloids in the subsequent steps. The *N*-alkyl-1-aza-3-dibenzylamino-spiro[4.5]-7-decen-2-ones are especially suitable for synthesis of FR901483 and TAN125D with the amine functionality in the right place. We are currently studying the application of this method for synthesis of natural spiro[cyclohexane-pyrrolidine] alkaloids and their analogs.

EXPERIMENTAL

Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying reagents immediately prior to use. Tetrahydrofuran and ether were distilled from sodium and benzophenone under argon. Toluene, triethylamine, and dichloromethane were distilled from calcium hydride under argon. Moisture- and air-sensitive reactions were carried out under an atmosphere of argon. Reaction flasks and glassware were oven-dried at 105 °C overnight. Unless otherwise stated, concentration was performed under reduced pressure. Analytical thin-layer chromatography (TLC) was conducted using Fluka precoated TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Compounds were visualized by ultraviolet light and/or by heating the plate after dipping in a 1% solution of vanillin in 0.1 M sulfuric acid in EtOH. Flash chromatography was carried out using Scientific Absorbents Inc. silica gel (40 μm particle size). Optical rotations were measured with a Perkin-Elmer 243 polarimeter at ambient temperature using a 1 dm cell with 1 mL capacity. Infrared (IR) spectra were recorded on a Nicolet 5DXB FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using a Bruker Avance-300 spectrometer. ESI-HRMS's were analyzed with Agilent 6550 iFunnel Q-TOF LC/MS system by Science Laboratory Center, Naresuan University.

N,N-Dibenzyl-L-aspartic acid (17)

To a solution of L-aspartic acid (5.00 g, 37.6 mmol) in MeOH (50 mL) and H_2O (50 mL) were added NaOH (3.93 g, 98.2 mmol), K_2CO_3 (13.57 g, 98.2 mmmol) and benzyl chloride (18.4 mL, 160 mmol). The mixture was heated to reflux at 95 °C overnight and allowed to cool to room temperature. Subsequently the mixture was acidified with 1 M HCl (pH = 2). Within 2 h, *N,N*-dibenzyl-L-aspartic acid (**17**) precipitated from the reaction mixture upon standing (11.8 g, quantitative) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.40 (brs, 2H), 7.40-7.19 (m, 10H), 3.72 (d, *J* = 14.0 Hz, 2H), 3.64-3.54 (m, 3H), 2.76 (dd, *J* = 16.0, 9.1 Hz, 1H), 2.55 (dd, *J* = 16.0, 5.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.2, 172.9, 139.7 (2C), 128.9 (4C), 128.7 (4C), 127.4 (2C), 58.2, 54.58 (2C), 34.5; $[\alpha]_{25}^{D}$ –40.6 (*c* 1.1, MeOH); ν_{max} (film) 1751, 1599,

1229, 1170, 1081, 987, 888 cm^{-1}; ESI-HRMS calculated for $C_{18}H_{19}NNaO_4$ $[M+Na]^+$ 336.1206, found 336.1208.

(*S*)-1-Allyl-3-(dibenzylamino)pyrrolidine-2,5-dione (18)

To a solution of *N*,*N*-dibenzylaspartic acid **17** (1.25 g, 3.98 mmol) in dry CH_2Cl_2 (50 mL) under argon atmosphere were added allylamine (0.31 mL, 4.2 mmol), CDI (1.33 g, 8.2 mmol), DMAP (100 mg, 0.82 mmol) and Et_3N (1.14 mL, 8.2 mmol) and the mixture was stirred for 16 h at room temperature. To this mixture was added water (50 mL) and phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give *N*-allyl-3-dibenzylaminosuccinimide **18** (1.13 g, 85%) as a green oil: R_f (4:1 hexane/EtOAc) 0.53; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.0 Hz, 2H), 7.35-7.20 (m, 6H), 5.75 (ddt, *J* = 15.9, 10.1, 7.1 Hz, 1H), 5.20 (d, *J* = 15.9 Hz, 1H), 5.12 (d, *J* = 10.1 Hz, 1H), 4.10 (d, *J* = 7.1 Hz, 2H), 3.89 (dd, *J* = 8.9, 5.5 Hz, 1H), 3.80 (d, *J* = 13.4 Hz, 2H), 3.61 (d, *J* = 13.4 Hz, 2H), 2.71 (dd, *J* = 18.5, 8.9 Hz, 1H), 2.58 (dd, *J* = 18.5, 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 174.6, 138.2 (2C), 130.7, 129.6 (4C), 129.1 (4C), 127.4 (2C), 118.5, 57.4, 54.6 (2C), 40.6, 32.1; $[\alpha]_{25}^{D}$ –8.3 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3086, 3028, 2928, 2853, 1777, 1699, 1391, 1330, 1194, 741, 697 cm^{-1}; ESI-HRMS calculated for $C_{21}H_{23}N_2O_2$ $[M+H]^+$ 335.1754, found 335.1759.

(*S*)-1-(3,4-Dimethoxyphenylethyl)-3-(dibenzylamino)pyrrolidine-2,5-dione (19)

To a solution of *N*,*N*-dibenzyl-L-aspartic acid **17** (1.02 g, 3.25 mmol) in dry CH_2Cl_2 (40 mL) under argon atmosphere were added homoveratrylamine (0.58 mL, 3.43 mmol), CDI (1.09 g, 6.70 mmol), DMAP (82 mg, 0.67 mmol) and Et_3N (0.93 mL, 6.70 mmol) and the mixture was stirred for 16 h at room temperature. To this mixture was added water (30 mL) and phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give *N*-(3,4-dimethoxyphenylethyl)succinimide **19** (1.16 g, 78%) as a colorless oil: Rf (4:1 hexane/EtOAc) 0.45; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.16 (m, 10H), 6.81 (s, 1H), 6.62 (d, *J* = 8.2 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 3.88-3.70 (m, 3H), 3.85 (s, 3H), 3.71 (s, 3H), 3.62 (d, *J* = 13.5 Hz, 2H), 3.46 (d, *J* = 13.5 Hz, 2H), 2.87 (t, *J* = 7.6 Hz, 2H), 2.70 (dd, *J* = 18.4, 9.0 Hz, 1H), 2.53 (dd, *J* = 18.4, 5.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 175.1, 148.9, 147.8, 138.1, 129.8, 128.8, 128.5, 127.5, 121.0, 111.9, 111.0, 57.2, 55.9, 55.7, 54.5, 39.4, 32.8, 32.0; $[\alpha]_{25}^{D}$ –10.2 (*c* 0.9, $CHCl_3$); ν_{max} (film) 2930, 1702, 1516, 1264, 1115, 699 cm^{-1}; ESI-HRMS calculated for $C_{28}H_{30}N_2NaO_4$ $[M+Na]^+$ 481.2103, found 481.2117.

(*S*)-1-(2-Bromo-4,5-dimethoxyphenylethyl)-3-(dibenzylamino)pyrrolidine-2,5-dione (20)

To a solution of *N*-(3,4-dimethoxyphenylethyl)-succinimide **19** (1.00 g, 2.18 mmol) in CH_2Cl_2 (50 mL) was added dropwise 2% bromine solution in CH_2Cl_2 (8.00 mL, 3.12 mmol) and the mixture was stirred for 2 h at room temperature. The solvent and residual bromine were evaporated under reduced pressure. The crude mixture was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give *N*-(2-bromo-4,5-dimethoxyphenylethyl)-3-dibenzylaminosuccinimide **20** (1.15 g, 98%) as a yellow oil: Rf (4:1 hexane/EtOAc) 0.65; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.16 (m, 10H), 6.88 (s, 1H), 6.71 (s, 1H), 3.88-3.70 (m, 3H), 3.85 (s, 3H), 3.71 (s, 3H), 3.62 (d, *J* = 13.5 Hz, 2H), 3.46 (d, *J* = 13.5 Hz, 2H), 2.87 (t, *J* = 7.6 Hz, 2H), 2.70 (dd, *J* = 18.4, 9.0 Hz, 1H), 2.53 (dd, *J* = 18.4, 5.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 174.9, 148.4, 148.3, 138.0, 129.8, 128.8 (4C), 128.7 (4C), 128.3, 127.6 (2C), 115.3, 114.4, 113.2, 57.4, 56.0, 55.8, 54.4 (2C), 38.0, 33.2, 31.7; $[\alpha]_{25}^{D}$ +36.0 (*c* 1.1, $CHCl_3$); ν_{max} (film) 2930, 1702, 1516, 1264, 1115, 1070, 699 cm^{-1}; ESI-HRMS calculated for $C_{28}H_{30}BrN_2O_4$ $[M+H]^+$ 537.1383, found 537.1391.

***N*,*N*-Dibenzyl-L-asparagine (21)**

To a solution of L-asparagine (5.00 g, 33.3 mmol) in MeOH and H_2O (1:1, 100 mL) was added NaOH (3.33 g, 83.3 mmol), K_2CO_3 (11.5 g, 83.8 mmol) and benzyl chloride (15.5 mL, 133 mmol). The mixture was heated to reflux at 95 °C overnight and subsequently acidified with 1 M HCl (pH = 2). The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 10:1 CH_2Cl_2/MeOH) to give *N*,*N*-dibenzyl-L-asparagine **21** (8.84 g, 85%) as a pale-yellow oil: R_f (10:1 CH_2Cl_2/MeOH) 0.36; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.13 (m, 10H), 6.00 (brs, 1H), 5.37 (brs, 2H), 5.30 (s, 2H), 4.08 (d, *J* = 13.4 Hz, 2H), 4.03-3.87 (m, 3H), 3.00 (dd, *J* = 16.3, 6.4 Hz, 1H), 2.72 (dd, *J* = 16.3, 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 172.3, 135.4 (2C), 129.6 (4C), 128.9 (4C), 128.3 (2C), 59.8, 54.8 (2C), 33.4; $[\alpha]_{25}^{D}$ –48.8 (*c* 1.7, $CHCl_3$); ν_{max} (film) 3192, 3064, 2924, 2852, 1669, 1495, 1456, 1365, 1285, 1182 cm^{-1}; ESI-HRMS calculated for $C_{18}H_{20}N_2NaO_3$ $[M+Na]^+$ 335.1366, found 335.1368.

(*S*)-3-(Dibenzylamino)pyrrolidine-2,5-dione (22)

To a solution of *N*,*N*-dibenzyl-L-asparagine **21** (1.24 g, 3.97 mmol) in dry CH_2Cl_2 (50 mL) under argon atmosphere were added CDI (0.97 g, 6.00 mmol), DMAP (73 mg, 0.60 mmol) and Et_3N (0.84 mL, 6.00 mmol) and the mixture was stirred for 16 h at room temperature. To this mixture was added water (20 mL) and phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 1:2 hexane/EtOAc) to give 3-

dibenzylaminosuccinimide **22** (1.10 g, 98%) as a white crystal: R_f (1:2 hexane/EtOAc) 0.31; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (brs, 1H), 7.43-7.14 (m, 10H), 3.91 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.81 (d, *J* = 13.5 Hz, 2H), 3.61 (d, *J* = 13.5 Hz, 2H), 2.61 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.71 (dd, *J* = 18.0, 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 178.6, 176.3, 176.2, 138.3 (2C), 128.9 (4C), 128.6 (4C), 127.6 (2C), 58.8, 54.7 (2C), 33.1; $[\alpha]_{25}^{D}$ –25.4 (*c* 1.6, $CHCl_3$); ν_{max} (film) 3234, 2923, 2849, 1782, 1705, 1494, 1454, 1338, 1191, 1165 cm^{-1}; ESI-HRMS calculated for $C_{18}H_{18}N_2NaO_2$ $[M+Na]^+$ 317.1260, found 317.1260.

(*S*)-3-(Dibenzylamino)-1-methylpyrrolidine-2,5-dione (23)

To a solution of 3-dibenzylaminosuccinimide **22** (583 mg, 1.98 mmol) in acetone (30 mL) were added dimethyl sulfate (0.30 mL, 3.16 mmol) and K_2CO_3 (437 mg, 3.16 mmol) and the mixture was stirred for 16 h. The mixture was filtered under reduced pressure and to the filtrate was added water (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water (2 × 30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained without purification as *N*-methyl-3-dibenzylaminosuccinimide **23** (561 mg, 92%) as a green oil: R_f (4:1 hexane/EtOAc) 0.63; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.20 (m, 10H), 3.93 (dd, *J* = 8.9, 5.4 Hz, 1H), 3.83 (d, *J* = 13.4 Hz, 2H), 3.64 (d, *J* = 13.4 Hz, 2H), 2.95 (s, 3H), 2.74 (dd, *J* = 18.5, 8.9 Hz, 1H), 2.61 (dd, *J* = 18.5, 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 175.2, 138.2 (2C), 128.8 (4C), 128.6 (4C), 127.4 (2C), 57.5, 54.6 (2C), 31.8, 24.3; $[\alpha]_{25}^{D}$ –5.5 (*c* 1.3, $CHCl_3$); ν_{max} (film) 3082, 3029, 2941, 2847, 1770, 1702, 1360, 1195, 1130, 698 cm^{-1}; ESI-HRMS calculated for $C_{19}H_{21}N_2O_2$ $[M+H]^+$ 309.1598, found 309.1603.

(*S*)-3-(Dibenzylamino)-1-(prop-2-ynyl)pyrrolidine-2,5-dione (24)

To a solution of 3-dibenzylaminosuccinimide **22** (298 mg, 1.01 mmol) in DMF (10 mL) under argon atmosphere at room temperature were added K_2CO_3 (166 mg, 1.20 mmol), KI (20 mg, 0.12 mmol) and propargyl bromide (80 wt% in toluene, 0.13 mL, 1.20 mmol) and the mixture was stirred for 3 h. To this mixture was added water (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 × 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give *N*-propargylsuccinimide **24** (299 mg, 89%) as a blue oil: R_f (4:1 hexane/EtOAc) 0.56; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.11 (m, 10H), 4.20 (d, *J* = 2.4 Hz, 2H), 3.92 (dd, *J* = 9.0, 5.3 Hz, 1H), 3.80 (d, *J* = 13.5 Hz, 2H), 3.63 (d, *J* = 13.5 Hz, 2H), 2.71 (dd, *J* = 18.6, 9.6 Hz, 1H), 2.59 (dd, *J* = 18.6, 5.3 Hz, 1H), 2.17 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 173.8, 138.1 (2C), 128.8 (4C), 128.5 (4C), 127.6 (2C), 77.0, 71.5, 57.5, 54.7, 32.4, 27.4; $[\alpha]_{25}^{D}$ –3.2 (*c* 2.0, $CHCl_3$); ν_{max} (film) 3280, 3029,

2939, 2847, 1774, 1702, 1398, 1360, 1195, 1130, 699 cm^{-1}; ESI-HRMS calculated for $C_{21}H_{21}N_2O_2$ $[M+H]^+$ 333.1598, found 333.1603.

(*S*)-1-(2-(5-Bromobenzo[*d*][1,3]dioxol-6-yl)ethyl)-3-(dibenzylamino)pyrrolidine-2,5-dione (25)

To a solution of 3-dibenzylaminosuccinimide **22** (300 mg, 1.02 mmol) in DMF (10 mL) under argon atmosphere at room temperature were added K_2CO_3 (169 mg, 1.22 mmol), KI (20 mg, 0.12 mmol) and 6-bromohomopiperonyl chloride (321 mg, 1.22 mmol) and the mixture was stirred for 8 h. To this mixture was added water (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 × 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give *N*-(6-bromohomopiperonyl)succinimide **25** (447 mg, 84%) as a green oil: R_f (2:1 hexane/EtOAc) 0.83; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.20 (m, 10H), 6.88 (s, 1H), 6.71 (s, 1H), 3.91-3.80 (m, 2H), 3.82 (s, 3H), 3.81-3.74 (m, 1H), 3.73 (s, 3H), 3.70 (d, *J* = 13.5 Hz, 2H), 3.52 (d, *J* = 13.5 Hz, 2H), 3.10-2.85 (m, 2H), 2.71 (dd, *J* = 18.6, 9.6 Hz, 1H), 2.60 (dd, *J* = 18.6, 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 175.1, 147.4 (2C), 138.4 (2C), 130.1, 128.5 (4C), 128.2 (4C), 127.5 (2C), 114.9, 112.8, 110.4, 101.8, 57.5, 54.5 (2C), 38.1, 33.7, 31.9; $[\alpha]_{25}^{D}$ +40.9 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3061, 3028, 2922, 1700, 1477, 1396, 1231, 1035, 736, 698 cm^{-1}; ESI-HRMS calculated for $C_{22}H_{24}N_2NaO_2$ $[M+Na]^+$ 371.1730, found 371.1725.

General procedure for reaction of *N*-alkyl-3-dibenzylaminosuccinimide with 4-pentenylmagnesium bromide

(3*S*)-3-(Dibenzylamino)-5-hydroxy-1-methyl-5-(pent-4-en-1-yl)pyrrolidin-2-one (26)

To a suspension of magnesium (1.2 g, 52 mmol) in EtO_2 (10 mL) was added 5-bromo-1-pentene in two portions (0.10 mL and 0.73 mL, 7 mmol) and the mixture was stirred for 20 min. The exothermic reaction caused boiling and refluxing of EtO_2. The mixture was cooled to –78 °C and a solution of *N*-methyl-3-dibenzylaminosuccinimide **23** (719 mg, 2.3 mmol) in CH_2Cl_2 (5 mL) was added under argon atmosphere. The mixture was stirred for 2 h. To this mixture was added sat. aq. NH_4Cl (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give *N*-methyl-γ-(pent-4-enyl)-γ-hydroxylactam **26** (688 mg, 79%) as a colorless oil: R_f (4:1 hexane/EtOAc) 0.33; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.14 (m, 10H), 5.74 (dddd, *J* = 17.1, 10.4, 7.1, 6.9 Hz, 1H), 5.01-4.89 (m, 2H), 3.89 (d, *J* = 13.8 Hz, 2H), 3.70 (d, *J* = 13.8 Hz, 2H), 3.61-3.44 (m, 1H), 2.69 (s, 3H), 2.35 (dd, *J* = 14.1, 9.4 Hz, 1H), 2.11-1.84 (m, 3H), 1.70 (td, *J* = 10.1, 5.4 Hz, 1H), 1.61-1.42 (m, 1H), 1.31-1.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 139.4 (2C), 137.8,

128.8 (4C), 128.6 (4C), 127.0 (2C), 115.3, 88.8, 59.3, 54.8 (2C), 37.1, 36.9, 33.3, 23.6, 22.8; $[\alpha]_{25}^{D}$ –17.3 (*c* 0.6, $CHCl_3$); ν_{max} (film) 3392, 2935, 1664, 1477, 1230, 1036, 699 cm^{-1}; ESI-HRMS calculated for $C_{24}H_{31}N_2O_2$ $[M+H]^+$ 379.2380, found 379.2386.

**In other cases, the crude hydroxylactam product was carried on to the next step without purification.*

General procedure for conversion of the hydroxylactam to 1-azaspiro[4.5]-7-decen-2-one via *N*-acyliminium spirocyclization

(*3S,5S*) -3-(Dibenzylamino)-1-methyl-1-azaspiro[4.5]-7-decen-2-one (31)

To a solution of hydroxylactam **26** (190 mg, 0.51 mmol) in dry CH_2Cl_2 (10 mL) under argon atmosphere at 0 °C was added TMSOTf (0.19 mL, 1.02 mmol) and the mixture was stirred for 3 h at 0 °C to room temperature. To this mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give 1-methyl-1-azaspiro[4.5]-7-decen-2-one **31** (145 mg, 79%) as pale-yellow oil: R_f (4:1 hexane/EtOAc) 0.54; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 6.4 Hz, 2H), 7.39-7.08 (m, 6H), 5.66 (d, *J* = 10.2 Hz, 1H), 5.52 (dt, *J* = 10.2, 1.8 Hz, 1H), 4.05 (d, *J* = 13.5 Hz, 2H), 3.89-3.70 (m, 3H), 2.75 (s, 3H), 2.28-2.14 (m, 4H), 2.00-1.82 (m, 1H) 1.74-1.54 (m, 1H), 1.43 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 140.0 (2C), 128.6, 128.4 (4C), 128.2 (4C), 126.9 (2C), 125.2, 59.7, 54.8 (2C), 32.9, 32.2, 32.1, 29.7, 23.3, 22.1; $[\alpha]_{25}^{D}$ +6.8 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3084, 3029, 2939, 2847, 1774, 1702, 1398, 1360, 1195, 1130 cm^{-1}; ESI-HRMS calculated for $C_{24}H_{29}N_2O$ $[M+H]^+$ 361.2274, found 361.2281.

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17. The ratio of the regioisomeric hydroxylactam products was determined by the integration of the ^{1}H NMR peaks of the crude product.