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A NEW SYNTHESIS OF (±)-CELACINNINE BY MEANS OF NON-SPERMIDINE-BASED METHODOLOGY

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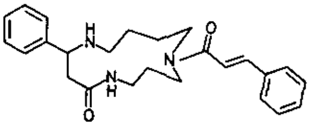
Abstract —— (±)-Celacinnine was synthesized relying on the novel methodology which features nucleophilic ring opening of 2-substituted 5,6-dihydro-4H-1,3-oxazine as a carboxamide synthon and requires neither spermidine nor amino acid condensation process for the lactam framework.

Celacinnine (**1**) was isolated from *Maytenus serrata* by Kupchan and co-workers[1] and belongs to the plant alkaloid derived from spermidine which is an important constituent of every living cell as spermine does so.[2] Because of the notable biological activity shown by members of these polyamine family,[3] an active effort has been made on the total synthesis of these natural products.[4] As far as **1** is concerned, three representative routes to **1** have proven to be fertile so far, that highlight 1) selective N-alkylation of spermidine and subsequent macrocyclization between amino- and tetrabutylammonium carboxylate-groups promoted by catecholborane,[5] 2) successive ring expansion through a transamidation process involving aminolactam,[6] and 3) stepwise manipulation of spermidine framework and final intramolecular aminolysis of aminoester system facilitated by boron-template,[7] respectively.

Recent effort in our laboratory to utilize 2-methyl-5,6-dihydro-4H-1,3-oxazine (**2**) as a potent secondary carboxamide building block[8] has prompted us to apply such idea to the total synthesis of **1** in order to test the feasibility of this strategy (Scheme 1) in the synthesis of polyamine lactam family. Retrosynthetic design based on the strategy is outlined in Scheme 2. This, if successful, would become an unprecedented method of polyamine lactam synthesis which requires neither spermi-



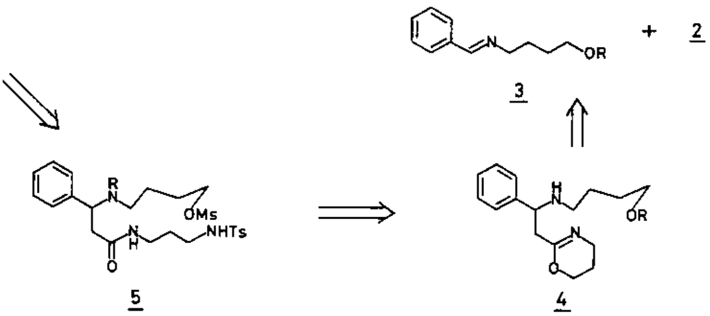
1

Scheme 1

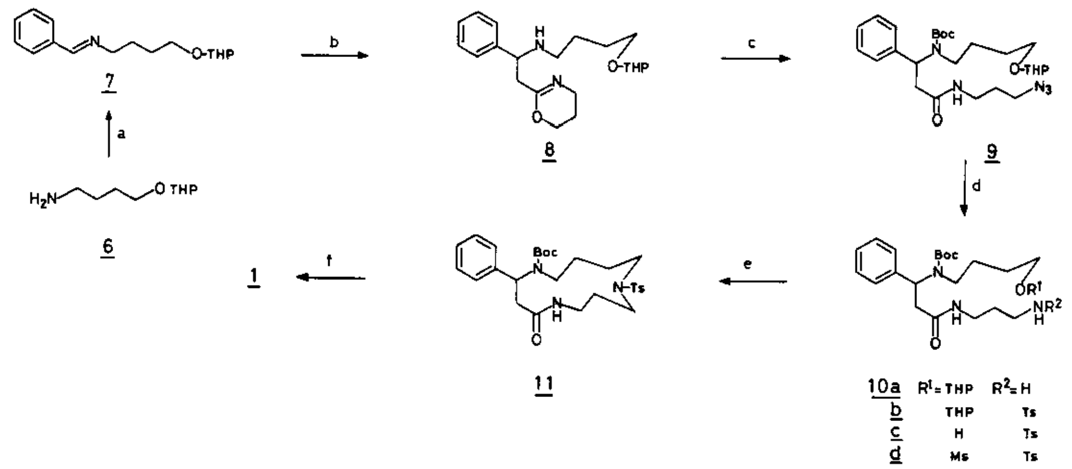
2

dine nor amino acid functionality and, in this respect, an ingenious device for the synthesis of related complex molecules, and, therefore, be highly useful. Here we will record the realization of this goal.

Scheme 2



Scheme 3



10	R^1	R^2
10a	THP	H
b	THP	Ts
c	H	Ts
d	Ms	Ts

a: $C_6H_5CHO/CH_2Cl_2/Na_2SO_4$/rt, 1 h (84%, dist) **b**: **2**/LDA/THF/-78°C, 0.5 h **c**: i)Boc_2O/CH_2Cl_2/rt, 10 h, ii)Me_3SiN_3/MeOH/DMF/70°C, 6 h (76% from **7**) **d**: i)H_2/Pd-C/EtOH/rt, 40 h, ii)TsCl/Et_3N/CH_2Cl_2/0°C, 15 min (66% from **9**), iii)TsOH/MeOH/rt, 1 h (98%), iv)MsCl/Et_3N/CH_2Cl_2/-10°C, 1.3 h (97%) **e**: K_2CO_3/CH_3CN/refl, 24 h (79%) **f**: i)+e/Pt-Hg/Me_4NCl/MeOH-CH_3CN/rt, ii) trans-cinnamoyl chloride/DMAP/CH_2Cl_2/rt, 8 h, iii)CF_3COOH/rt, 1 h (76% from **11**)

The requisite atom arrangement for **1** was envisaged to build up by a coupling of appropriate imine (**3**) with lithiated **2**. The adduct (**4**) reflects the desired celacinnine skeleton in the context of the transformation as indicated in Scheme 1. A macrocyclization, in this case, was expected to be realized through an intramolecular N-alkylation between toluenesulfonamide and methanesulfonate groups located at the both ends of the backbone as illustrated in Scheme 2 (the precursor (**5**)).[4i] Thus, the Schiff base (**7**) was prepared by simple mixing of 4-tetrahydropyranyloxy-butylamine (**6**)[9] with benzaldehyde in CH_2Cl_2 at room temperature in 84% yield after distillation. Well-known deprotonation of **2** [LDA/THF/-78°C] and subsequent reaction with **7** cleanly afforded the adduct (**8**), in which the amino group was protected with t-butyloxycarbonyl group (Boc) and thus-obtained intermediate was subjected to the chemical circumstances developed for nucleophilic ring opening of the oxazine moiety[8] to give N'-Boc-amino-N-(3'-azidopropyl)propionamide derivative (**9**) in 76% yield after silica gel chromatography. Because of unstability of a series of intermediates bearing oxazine moiety, a usual chromatographic purification had to be skipped during the conversion **7**→**9**. Nevertheless, **9** was easily purified (silica gel) and provided in a satisfactorily pure state as shown by carbon-13 nmr analysis,[10] and every functionality in this key intermediate was properly arranged.

The conversion of **9** to **10d**, an immediate precursor for macrocyclization, has been successfully performed by several routine chemical transformations. Thus, the azido group in **9** was reduced to amino group [H_2/Pd-C/EtOH, rt], which was mono-tosylated [TsCl/Et_3N/CH_2Cl_2, 0°C] to give **10b** in 66% yield (for two steps). The THP group was removed [TsOH/MeOH, rt] and the liberated hydroxyl group was sulfonylated [MsCl/Et_3N/CH_2Cl_2, -10°C] to furnish **10d** in 95% yield (for two steps) after silica gel chromatography. The stage was set for macrocyclization and, for this purpose, a diluted solution of **10d** in acetonitrile ([**10d**]=10^{-4}mol/l) was heated under reflux for 24 h in the presense of potassium carbonate to give the cyclized product (**11**) in 79% yield after silica gel chromatography. The N-tosyl group was splitted off by an electroreductive process [Pt-Hg/Me_4NCl/MeOH-MeCN, rt][11,4j] in almost quantitative yield and the required trans-cinnamoyl group was introduced to thus-generated amino group [trans-C_6H_5-CH=CH-COCl/DMAP/CH_2Cl_2, rt].[7] The final step leading to **1** was effected through a routine removal of the Boc group [CF_3COOH, rt] to give rise to the target molecule in 76% yield (from **11**) after silica gel chromatography. The synthetic (±)-celacinnine was identical with those of previously synthesized[5,6,7] in terms of mass, nmr, and ir spectra[12] and tlc behaviors of our sample with several solvent systems are completely identical with those of the authentic one.[13]

The present oxazine approach to the total synthesis of **1** has proved to be highly useful for the manipulation of spermidine-derived lactam framework. When we recall the previous success[4j] in the total synthesis of kukoamine A, one of acyclic spermine alkaloids, based on the similar strategy, the methodology described herein encourages us to apply this to the synthesis of other members of polyamine family and such is under active investigation in our laboratory.

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9) Prepared starting from 4-bromobutanol via a series of routine chemical transformation: i) DHP/PPTs/CH_2Cl_2, ii) NaN_3/EtOH-H_2O, and iii) H_2/Pd-C/EtOH.

10) Being consistent with the expected structure, twenty-two signals were observed: representative chemical shifts are 170.4 (s, CONH), 156.0 (s, NCOO), 140.1 (s, aryl-C), 128.4 (d, aryl-C),

127.4 (d, aryl-C), 127.0 (d, aryl-C), 98.79 (d, acetal-C), 79.92 (s, $O\underline{C}Me_3$), 56.68 (d, $Ph\underline{C}HN$), 28.36 (q, $C\underline{Me}_3$) plus twelve triplets ($CDCl_3$, 25 MHz).

11) L. Horner and H. Neumann, *Chem. Ber.*, 1965, **98**, 3462.

12) Analytical data for **1**: ir ($CHCl_3$) 3455, 3330, 1658(sh), 1649, 1599, 1559, 1497, 1430, 1115 cm^{-1}; nmr ($CDCl_3$, 400 MHz, 55°C) δ 7.70 (1H, d, J=15.4 Hz, $PhC\underline{H}=C$), 7.46-7.53 (2H, m, aryl-$\underline{H}$), 7.20-7.39 (9H, m, aryl-$\underline{H}$, $CON\underline{H}$), 6.82 (1H, d, J=15.4 Hz, $COC\underline{H}=C$), 3.99 (1H, t, J=7.4 Hz, $PhC\underline{H}N$), 3.60 (4H, m, $CH=CHCON(C\underline{H}_2)C\underline{H}_2$), 3.27-3.42 (1H, m, $CONHC(\underline{H})H$), 3.08-3.20 (1H, m, $CONHC(\underline{H})H$), 2.70 (1H, dt, J=12.1, 4.5 Hz, $CHNHC(\underline{H})H$), 2.52 (2H, d, J=7.4 Hz, $C\underline{H}_2CON$), 2.47 (1H, m, $CHNH\text{-}C(\underline{H})H$), 1.38-2.20 (7H, m, $CC\underline{H}_2$, $N\underline{H}$); mass m/z(%) 405(26), 274(72), 260(13), 172(10), 160(20), 156(13), 146(32), 132(19), 131(100), 103(63); exact mass m/z 405.2418 (calcd for $C_{25}H_{31}N_3O_2$, 405.2416). Spectral data for the synthetic intermediates leading to **1**: **7**; nmr ($CDCl_3$) δ 8.16 (1H, s), 7.51-7.80 (2H, m), 7.20-7.46 (3H, m), 4.50 (1H, s), 3.10-4.00 (6H, m), 1.20-2.10 (10H, m), ir (film) 1647 cm^{-1}. **8**; nmr ($CDCl_3$) δ 7.31 (5H, s), 4.52 (1H, s), 4.05 (2H, t, J=5.8 Hz), 3.02-3.24 (7H, m), 3.30 (2H, t, J=5.8 Hz), 2.39 (2H, d, J=6 Hz), 0.94-2.05 (13H, m), ir (film) 3330, 1680, 1457, 1355, 1240, 1129, 1079, 1032 cm^{-1}. **9**; nmr ($CDCl_3$) δ 7.28 (5H, s), 6.52 (1H, bs), 5.36 (1H, t, J=7.6 Hz), 4.46 (1H, s), 3.10-3.97 (8H, m), 2.69-3.10 (4H, m), 1.49 (9H, s), 1.08-1.96 (12H, m), ir (film) 3330, 2204, 1690, 1650 cm^{-1}. **10a**; nmr ($CDCl_3$) δ 7.30 (5H, s), 6.86 (1H, bs), 5.38 (1H, t, J=7.6 Hz), 4.50 (1H, s), 2.72 (2H, t, J=6.6 Hz), 2.79-3.90 (10H, m), 1.75 (2H, s), 1.45 (9H, s), 1.00-2.06 (12H, m), ir ($CHCl_3$) 3470, 3340, 1675, 1659(sh), 1368, 1162, 1140 cm^{-1}. **10b**; nmr ($CDCl_3$) δ 7.76 (2H, d, J=8.2 Hz), 7.29 (5H, s), 7.28 (2H, d, J=8.2 Hz), 6.57 (1H, bt, J=6.0 Hz), 5.88 (1H, bt, J=6.4 Hz), 5.38 (1H, bt, J=7 Hz), 4.49 (1H, s), 2.56-4.16 (12H, m), 2.38 (3H, s), 1.43 (9H, s), 1.14-1.89 (12H, m), ir (film) 3320, 3260, 1685, 1660(sh), 1370, 1165 cm^{-1}. **10c**; mp 173-175°C, nmr ($CDCl_3$) δ 7.75 (2H, d, J=8.3 Hz), 7.29 (7H, s and d, J=8.3 Hz), 6.64 (1H, bs), 6.05 (1H, bs), 5.36 (1H, m), 3.55 (2H, m), 2.63-3.42 (8H, m), 2.41 (3H, s), 1.44 (9H, s), 1.05-1.80 (7H, m), ir (KBr) 3560, 3375, 3180, 1665, 1569 (sh), 1322, 1162 cm^{-1}. **10d**; nmr ($CDCl_3$) δ 7.69 (2H, d, J=8.2 Hz), 7.22 (7H, s and d, J=8.2 Hz), 6.54 (1H, bt), 6.01 (1H, t, J=6.0 Hz), 5.40 (1H, m), 4.09 (2H, dt), 2.95 (3H, s), 2.52-3.50 (8H, m), 2.39 (3H, s), 1.42 (9H, s), 1.09-1.89 (6H, m), ir (film) 3380, 3280, 1679, 1659(sh), 1325, 1172, 1160 cm^{-1}. **11**; mp 207-208°C, nmr ($CDCl_3$) δ 7.67 (2H, d, J=8.6 Hz), 7.20-7.45 (7H, m), 6.70 (1H, bs), 4.85-6.18 (1H, very bs), 2.50-4.22 (10H, m), 2.43 (3H, s), 1.50 (9H, s), 1.10-2.11 (6H, m), ir ($CHCl_3$) 3460, 1680, 1660(sh), 1339, 1161 cm^{-1}.

13) The authentic (±)-celacinnine was provided through the courtesy of Professor H. Yamamoto and Dr. K. Maruoka (reference 7): Rf values (silica gel, Merck 60 F_{254}, 0.25 mm thick); 0.09 (EtOAc), 0.35 (EtOAc-MeOH, 15:1), 0.38 ($CHCl_3$-MeOH, 10:1) and 0.53 (acetone).

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