Synthesis of 4-Dendronized β-Lactams

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Abstract: The first synthesis of 4-dendronized β-lactams using the standard Staudinger ketene–imine cyclization is described. Both π-conjugated and Fréchet's aromatic polyether dendrons having imine focal points were used as starting materials. Exclusive *cis*-stereochemistry was observed for all the β-lactams prepared.

Key words: dendrimers, β-lactams, imines, ketenes, Staudinger reaction

Dendrimers are a unique class of compounds, which have been largely studied during the last two decades. Synthetic methodologies for dendrimers are well known[1] and the wide scope of their applications is continuously growing.[2] One of the more promising field for dendrimers is their use for biomedical applications. Their ability to be used for diagnostics and therapy (including magnetic resonance imaging, drug-delivery, DNA biosensors, boron neutron-capture therapy, etc.), and as new polymeric biomaterials for tissue engineering, has been recently reviewed.[3]

On the other hand, the synthesis of new 2-azetidinone derivatives is a permanent goal[4] because of the wide presence of this ring in antibiotics, the increased bacterial-resistance to natural β-lactam antibiotics and, more recently, the development of nonantibiotic uses.[5]

Thus, dendronized β-lactams would incorporate in a unique structure two of the most interesting classes of compounds. However, surprisingly, β-lactams having dendritic substituents attached to the four-membered ring have not been reported yet. To the best of our knowledge, there are only two papers where dendrimers and β-lactams are related. One of them describes the use of a carbosilane dendrimer for the synthesis of a library of β-lactams;[6] the other one concerns the use of PAMAM for preparing densely penicilloylated dendrimers.[7]

Herein we describe the first synthesis of a set of β-lactams that incorporates different dendritic wedges (up to third generation) at the 4-position of the 2-azetidinone ring. The synthesis has been envisaged following the classical Staudinger approach based on the reaction of imines and ketenes.[8]

The required dendritic imines were prepared from both π-conjugated dendrons, previously reported by us,[9] and Fréchet's type dendrons[10] having formyl focal points. Classical condensation of the dendritic aldehydes with a slight excess of *p*-anisidine in CH_2Cl_2 in the presence of molecular sieves (4 Å) afforded smoothly the expected dendritic imines (Table 1).[11] Purification of these compounds was performed easily and efficiently by washing the crude product with ethanol in order to solubilize the excess of amine, and filtering off the pure desired imine.

The synthesis of the 4-dendronized β-lactams was achieved following a standard methodology.[8b] Thus, treatment of imines **1a**,**b** with isobutyryl chloride and phenoxyacetyl chloride, respectively, in dichloromethane at room temperature and in the presence of triethylamine gave β-lactams **2a**,**b**. In addition, enantiomerically pure 2-azetidinones **2c**–**f**[12] were obtained from (+)-(*S*)-(4-phenyl-2-oxo-1,3-oxazolidin-3-yl)acetic acid and the corresponding imines **1b**–**e** in the presence of triethylamine and dichlorophenylphosphate as condensating agent in the same solvent (Table 2).

It is noteworthy that exclusive *cis*-stereochemistry was observed for all β-lactams **2** prepared as determined by high field ^{1}H NMR analysis of the crude reaction mixtures. It was established by the value of coupling constants of the H3-H4 protons (J = ca. 5 Hz). No traces of the *trans*-isomers were detected in any case. As exemplified by compound **2f**, the stereochemical outcome of the reaction did not suffer any variation even with substituents as large as a third generation Fréchet dendron.

The clean and high efficiency of the reactions employed facilitated product isolation and purification. The structure and purity of all the new compounds described herein has been confirmed using MS, NMR, IR, and elemental analysis. HRMS analyses of **2a**,**b**,**e** gave the expected molecular ions. The MALDI-TOF spectra of **2c**,**d**,**f** showed peaks matching the calculated values for the expected molecular weights (Table 3).

In conclusion, we have demonstrated that the standard Staudinger ketene–imine cyclization can be used to efficiently prepare in a complete stereoselective manner the hitherto unknown *cis*-3-substituted-4-dendronized β-lactams **2**. This strategy is extremely general, permitting not only the use of different ketene derivatives as starting materials but also the introduction at the 4-position of the 2-azetidinone ring of both π-conjugated and Fréchet's type dendritic branches.

Further transformations and applications of the prepared dendronized β-lactams are currently investigated in our laboratories.

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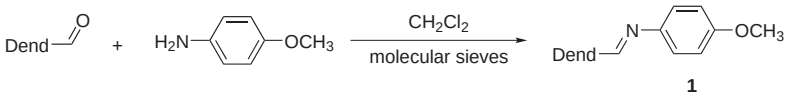
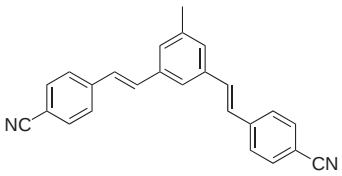
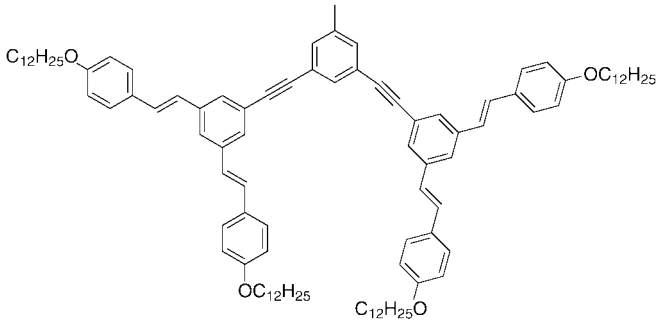
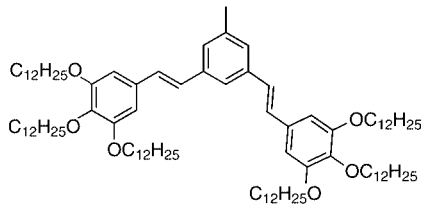
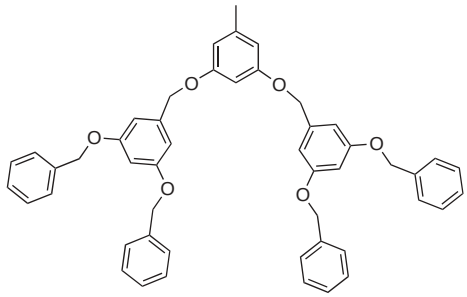
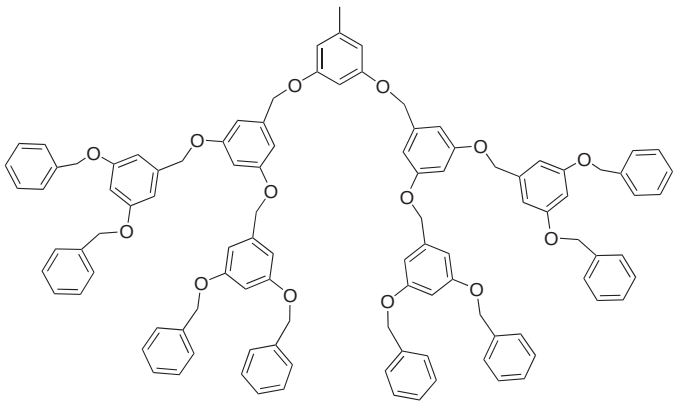
Table 1 Preparation of Dendritic Imines

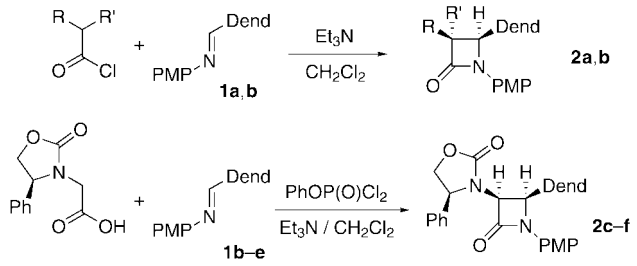


1

Entry	Dend	Imine	Yield (%)[a]
1		**1a**	81
2		**1b**	87
3		**1c**	98
4		**1d**	92
5		**1e**	85

[a] Not optimized isolated yields.

Table 2 Preparation of 4-Dendronized β-Lactams



Entry	R	R′	Starting Imine	β-Lactam	Yield (%)[a]	$[\alpha]_D^{20}$ (CH_3Cl)[c]
1	CH_3	CH_3	**1a**	**2a**	92	–
2	PhO	H	**1b**	**2b**	80	–
3	*S*-Ox[b]	H	**1c**	**2c**	75	+32.9° (*c* 0.07)
4	*S*-Ox[b]	H	**1b**	**2d**	90	–1.7° (*c* 1.18)
5	*S*-Ox[b]	H	**1d**	**2e**	72	+49.0 (*c* 0.05)
6	*S*-Ox[b]	H	**1e**	**2f**	54	+29.0 (*c* 0.03)

[a] Not optimized isolated yields.
[b] *S*-Ox = (*S*)-4-phenyl-2-oxo-1,3-oxazolidin-3-yl.
[c] Concentration in g/100 mL

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Table 3 Mass Spectrometry of Compounds **1** and **2**

Entry	Compound	Molecular Formula	Method[a]	Found	MW Calcd
1	**1a**	$C_{32}H_{23}N_3O$	EI+, HRMS	465.2 [M^+], 465.1834	465.55, 465.1841
2	**1b**	$C_{110}H_{141}NO_5$	FAB+, HRMS	1556.8 [M^+], 1556.0797	1557.33, 1556.0810
3	**1c**	$C_{102}H_{169}NO_7$	FAB+, HRMS	1520.7 [M^+], 1520.2836	1521.47, 1520.2899
4	**1d**	$C_{56}H_{49}NO_7$	EI+, HRMS	847.6 [M^+], 847.3509	848.01, 847.3498
5	**1e**	$C_{112}H_{97}NO_{15}$	MALDI	1719.8 [M + Na]$^+$	1697.00
6	**2a**	$C_{36}H_{29}N_3O_2$	EI+, HRMS	535.65 [M^+], 535.2262	535.65, 535.2260
7	**2b**	$C_{118}H_{147}NO_7$	FAB+, HRMS	1691.6 [M^+], 1690.1136	1691.47, 1690.1178
8	**2c**	$C_{113}H_{178}N_2O_{10}$	MALDI	1724.2 [M^+]	1724.66
9	**2d**	$C_{121}H_{150}N_2O_8$	MALDI	1783.1 [M + Na]$^+$	1760.53
10	**2e**	$C_{67}H_{58}N_2O_{10}$	FAB+, HRMS	1051.2 [M^+], 1050.4055	1051.20, 1050.4091
11	**2f**	$C_{123}H_{106}N_2O_{18}$	MALDI	1922.7 [M + Na]$^+$	1900.20

[a] FAB+: matrix of *m*-nitrobenzyl alcohol; MALDI-TOF: matrix of dithranol in the presence of NaI. Spectrum for **2c** could be recorded without Na^+ ions.

(10) Pollak, K. W.; Sanford, E. M.; Fréchet, J. M. J. *J. Mater. Chem.* **1998**, *8*, 519. Alternatively, we have obtained second and third generation Fréchet's dendrons having formyl focal points by oxidation with MnO_2 in CH_2Cl_2 of the corresponding dendrons having hydroxymethyl focal points.

(11) **Representative Experimental Procedure for the Preparation of Imine 1b:** A solution of the starting aldehyde (300 mg, 0.21 mmol) and *p*-anisidine (51 mg, 0.41 mmol) in dry CH_2Cl_2 (10 mL) was stirred overnight under argon at r.t. over molecular sieves (4 Å). Then, the molecular sieves were removed by filtration and the solvent was evaporated in vacuo. The residue was washed with EtOH in order to solubilize the excess of *p*-anisidine, and the insoluble imine **1b** was obtained by filtration as a yellow solid (280 mg, 87% yield). Further purification could be obtained by crystallization from $CHCl_3$/EtOH. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 12H, 4 × CH_3), 1.20–1.50 (m, 72 H, 36 × CH_2), 1.79 (m, 8 H, 4 × CH_2), 3.85 (s, 3 H, OCH_3), 3.98 (t, 8 H, *J* = 6.6 Hz, 4 × CH_2), 6.90–7.00 (m including A of ABq, 14 H, *J* = 8.7 Hz, 4 × CH= and arom.), 7.14 (B of ABq, 4 H, *J* = 16.5 Hz, 4 × CH=), 7.29 (B of ABq, 2 H, *J* = 8.7 Hz, arom.), 7.47 (B of ABq, 8 H, *J* = 8.7 Hz, arom.), 7.54 (s, 2 H, arom.), 7.55 (s, 4 H, arom.), 7.83 (t, 1 H, *J* = 1.5 Hz, arom.), 8.04 (d, 2 H, *J* = 1.5 Hz, arom.), 8.47 (s, 1 H, CH=N). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ = 159.1 (C), 158.6 (C), 156.2 (CH), 144.2 (C), 138.2 (C), 136.9 (C), 136.4 (CH), 131.2 (CH), 129.5 (C), 129.3 (CH), 127.8 (CH), 127.7 (CH), 125.3 (CH), 124.6 (CH), 124.2 (C), 123.3 (C), 122.4 (CH), 114.7 (CH), 114.4 (CH), 90.7 (C), 88.0 (C), 68.1 (OCH_2), 55.5 (OCH_3), 31.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.0 (CH_2), 22.7 (CH_2), 14.1 (CH_3). IR (KBr): ν = 1618 (C=N), 1585, 1512, 1466, 1256 cm^{-1}. MS (FAB+): *m/z*= 1556.8. HRMS: *m/z* calcd for $C_{110}H_{141}NO_5$: 1556.0810. Found: 1556.0797. Anal. Calcd for $C_{110}H_{141}NO_5$: C, 84.84; H, 9.13; N, 0.90. Found: C, 84.47; H, 9.29; N, 0.81.

(12) **Representative Experimental Procedure for the Preparation of β-Lactam 2f:** To a cooled solution (0 °C) under argon of imine **1e** (100 mg, 0.06 mmol) and (+)-(*S*)-(4-phenyl-2-oxo-1,3-oxazolidin-3-yl)acetic acid in Et_3N (1 mL) and dry CH_2Cl_2 (3 mL) was added dropwise dichlorophenylphosphate (14 μL, 0.09 mmol). The cooling bath was removed and the mixture was stirred at r.t. for 24 h. Finally, it was quenched with 1 M HCl, extracted with CH_2Cl_2 (×3), and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, CH_2Cl_2) to give **2f** as a white solid (60 mg, 54% yield). $[\alpha]_D^{20}$ = +29.0 (*c* 0.03, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.67 (s, 3 H, OCH_3), 3.88 (dd, 1 H, *J* = 8.5 Hz, *J* = 7.5 Hz, CH-O), 4.20 (t, 1 H, *J* = 9.0 Hz, Ph-CH-N), 4.35 (dd, 1 H, *J* = 8.5 Hz, *J* = 7.5 Hz, CH-O), 4.54 (d, 1 H, *J* = 5.0 Hz, H4), 4.89–5.02 (m including d, 29 H, *J* = 5.0 Hz, H3 and 14 × CH_2), 6.47 (br s, 2 H, arom.), 6.49 (d, 2 H, *J* = 2.0 Hz, arom.), 6.56 (t, 4 H, *J* = 2.0 Hz, arom.), 6.61 (t, 1 H, *J* = 2.0 Hz, arom.), 6.64 (d, 4 H, *J* = 2.0 Hz, arom.), 6.67 (d, 8 H, *J* = 2.0 Hz, arom.), 6.70 (A of ABq, 2 H, *J* = 9.0 Hz, arom.), 7.08–7.11 (m, 2 H, arom.), 7.18 (B of ABq, 2 H, *J* = 9.0 Hz, arom.), 7.28–7.42 (m, 43 H, arom.). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 160.1 (C), 160.0 (C), 159.9 (C), 156.9 (C), 156.2 (C), 139.2 (C), 139.1 (C), 136.7 (C), 136.5 (C), 135.2 (C), 130.8 (C), 129.3 (CH) 129.2 (CH), 128.6 (CH), 128.0 (CH), 127.6 (CH), 118.4 (CH), 114.1 (CH), 106.4 (CH), 106.2 (CH), 106.1 (CH), 103.1 (CH), 101.5 (CH), 101.4 (CH), 70.2 (CH_2), 70.0 (CH_2), 69.9 (CH_2), 69.8 (CH_2), 62.5 (CH), 61.3 (CH), 59.6 (CH), 55.3 (OCH_3). IR (KBr): ν = 1754 (C=O), 1596 cm^{-1}. MS (MALDI-TOF): *m/z* = 1922.7 (M + Na), 1497.5, 1027.1. Anal. Calcd for $C_{123}H_{106}N_2O_{18}$: C, 77.75; H, 5.62; N, 1.47. Found: C, 77.42; H, 5.71; N, 1.43.