A Tunable One-Step *N*,*N*′-Disubstitution of 1,4,8,11-Tetraazacyclotetradecane with Acrylamide

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N,*N*′-disubstitution of cyclam without the use of protecting groups was investigated. This macrocycle reacted with two equivalents of a Michael acceptor in chloroform to yield as a major isolated compound the 1,8 di-*N*,*N*′-substituted macrocycle. Running the same reaction in the presence of one equivalent of *para*-toluenesulfonic acid led to the 1,11-di-*N*,*N*′-substituted macrocycle as the major product. Each regioisomer has been isolated and fully characterized. The observed regioselectivity is discussed with respect to the reactivity of the unprotonated or protonated monoalkylated intermediate. A site of protonation for the latter intermediate is deduced from an NMR study.

Introduction

The many potential applications of functionalized azamacrocycles in coordination chemistry, for biomedical applications or in the field of radiotherapy, have made them very attractive targets.[1,2] Selective introduction of two substituents on the nitrogen atoms of tetraazamacrocycles remains a challenging problem. While mono or tetra *N*-substitution affords a single product, several di-substitution patterns exist and, for example, in the case of 1,4,8,11-tetraazacyclotetradecane or cyclam there are three possible constitutional isomers.

Existing approaches toward regioselective disubstitution have involved multi-step processes with protecting groups starting from the tetraazamacrocycle. Regioselective tosylation[3] or reaction with $(Boc)_2O$[4] led after alkylation and deprotection to 1,8-dialkylated derivatives of cyclam.[4,5] Tetraazamacrocycles in which N^1 and N^{11} amine sites are connected through aminal[6] or formamidinium salt[7] type bridges have been used as key intermediates in the synthesis of several 1,11 derivatives of cyclam.[6,7,8] A bis-aminal compound derived from cyclam forming exclusively six-membered rings[9] has been synthesized and, after additional steps, led to symmetrical[10,11] and disymmetrical[12] 1,8-disubstituted macrocycles. Similarly, an intermediate cross-bridged cyclam obtained from cyclam and glyoxal led to 1,8-derivatives of cyclam.[13,14] Alternatively, 1,8-disubstituted macrobicyclic[15] and macrocyclic[8] derivatives of cyclam have been obtained from 5,12-dioxocyclam. Finally, under high dilution conditions, direct reaction of cyclam with bis-electrophiles gave macrobicyclic ligands possessing tertiary amines at N^1 and N^8.[16,17]

Another approach toward selective functionalization, without protection, relies on the unusual properties of tetraazamacrocycles which have two basic and two nonbasic nitrogen atoms so that two nitrogen atoms can be temporarily protected by protons. A pH-controlled reaction between 1,4,7,10-tetraazacyclododecane (cyclen) and chloroformates has been achieved at an appropriate pH (pH = 2−3).[18,19] Previously, we have shown that in the presence of one equivalent of *para*-toluenesulfonic acid (PTSA) addition of cyclam to Michael acceptors affords selective access to various monosubstituted derivatives.[20,21] In this paper, we show that disubstituted cyclam derivatives are similarly obtained in a one-step process involving a controlled Michael addition and, moreover, that the regioselectivity of the diaddition can be tuned by the presence of acid.

Results

The reaction of cyclam in chloroform with two equivalents of acrylamide led to a mixture of two *N*,*N*′-disubstituted derivatives: the 1,8-regioisomer **1** as a major product and the 1,11-regioisomer **2** as a minor product. Separation through column chromatography afforded **1** and **2** in 43 and 18% yields respectively. The ratio of the isolated regioisomers **1/2** is 70:30 (Figure 1). On the other hand, when the reaction was run in the presence of one equivalent of *para*-toluenesulfonic acid, a change in the regioselectivity occurred: the major product turned out to be the 1,11-disub-

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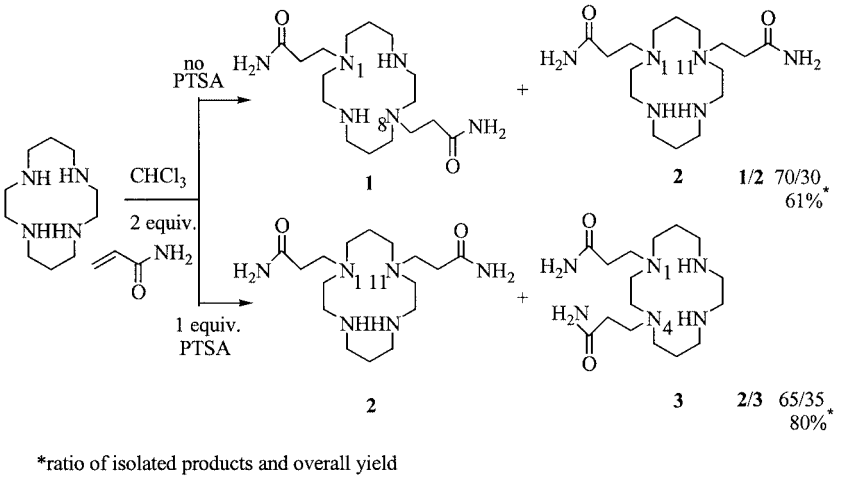


Figure 1. Synthesis of di-*N*,*N*′-substituted derivatives of cyclam

stituted macrocycle **2** together with the 1,4-regioisomer **3**. The regioisomers **2** and **3** were isolated after column chromatography in 50 and 30% yields, respectively. The ratio of the isolated regioisomers **2/3** is 65:35. Under the two sets of conditions described above, tri-, or tetrasubstituted derivatives have not been formed, while unchanged cyclam and traces of monosubstituted cyclam have been isolated. Moreover, in each case, only two disubstituted products were formed; the third regioisomer was not detected.

It is worth noticing that these reactions are conveniently followed by thin-layer chromatography (TLC): the use of an ethanolic solution of copper nitrate as a revelator allows one to determine the substitution patterns since each regioisomer gives a distinctive colored spot: pink for the 1,8-disubstituted compound **1**, in agreement with previously reported spectroscopic data for the 1,8-dimethylcyclam copper complex,[5] blue and purple respectively for the 1,11- and the 1,4-regioisomers **2** and **3**.

All three regioisomers have been characterized and their disubstitution patterns determined by NMR spectroscopy. The observed number of ^{1}H NMR signals is in agreement with the symmetry of the macrocycles (Figure 2). Complete assignments in the ^{1}H NMR spectra have been inferred from COSY experiments and/or homonuclear irradiations assuming that methylene groups *a* or *b* adjacent to tertiary amines are found at higher field than methylene groups *c* or *d* close to secondary amines, as was observed in the case of the corresponding monosubstituted cyclam.[20] Compound **2** is the only one that possesses two high-field resonances at δ = 1.64 and 1.77 ppm attributed to the center methylenes *e* and *f* of the two different propylene linkages while spectra of both **1** and **3** indicate the presence of only

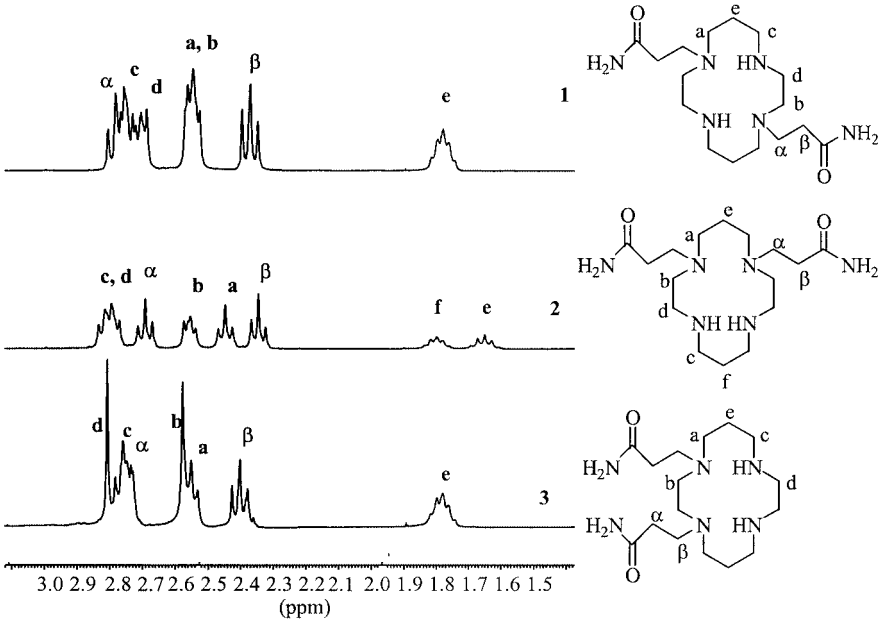
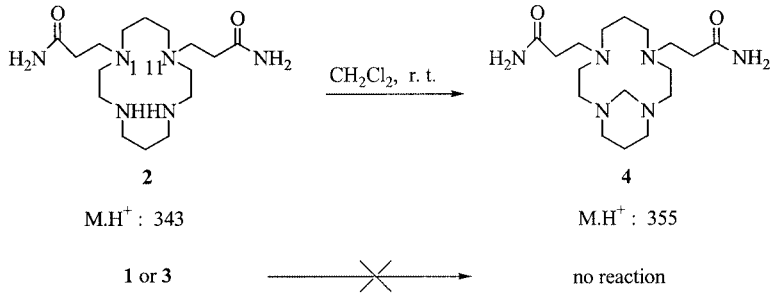


Figure 2. ^{1}H NMR spectra (300 MHz, 25 °C, $CD_3OD/CDCl_3$, 7:1) of **1**, **2**, and **3**



Scheme 1

one type of propylene bridge *e*. Finally the spectrum of **3** exhibits the expected two singlets,[22] each corresponding to protons of one ethylenic bridge *b* and *d*. Accordingly, the ^{13}C NMR spectra of compounds **1** and **3** possess seven aliphatic signals while compound **2** shows eight signals including two high-field resonances for non-equivalent central methylenes *e* and *f*.

Finally, cyclam has been reported to give a 1,11-methylene-bridged compound in dichloromethane.[6] Accordingly, reaction of *N*,*N*′-disubstituted compounds **1**, **2**, and **3** with CH_2Cl_2 confirms the observed disubstitution patterns. While both the 1,8 and 1,4 derivatives **1** and **3** do not react, the 1,5 disubstituted compound **2** undergoes the bridging reaction with CH_2Cl_2 to give the methylene-bridged hexahydropyrimidine **4** (Scheme 1). Formation of **4** was checked by mass spectrometry, in the electrospray mode. The product shows the expected *m*/*z* peak at 355 (**4**·H$^+$) in its mass spectrum compared to the *m*/*z* peak at 343 (**2**·H$^+$) for the starting compound. Interestingly, this reaction with CH_2Cl_2 coupled with mass spectrometry can be used to detect the presence of the 1,11 regioisomer in reaction mixtures.

Thus, the Michael addition of cyclam on acrylamide is a versatile method that allows one to synthesize all three regioisomers of disubstituted cyclam, with acceptable preparative yields, simply by running the reaction in $CHCl_3$ with or without PTSA. Furthermore, the regioselective features of this reaction appear to be quite general since the nucleophilic addition of cyclam to hindered tertiary acrylamides, such as *N*-alkylglucosylacrylamides,[23] exhibits the same selectivity patterns in $CHCl_3$: in the presence of one equivalent of PTSA, the reaction of cyclam with *N*-dodecylglucosylacrylamide gives a mixture of 1,11 and 1,4 isomers in about 60:40 molar ratio and 85% overall yield while in pure chloroform the 1,8-diadduct is the major product.

Discussion

In pure chloroform, the formation of the less-hindered 1,8-diadduct **1** as the major product is in good agreement with the greatest reactivity of the two trans nitrogen atoms deduced from Molecular Electrostatic Potential values.[17] Assuming a stepwise reaction, the formation of **1** results from a second addition trans to the substituent on the monosubstituted intermediate **5**. Indeed 3-(1,4,8,11-tetraazacyclotetradecan-1-yl)propionamide[20] (**5**) was observed on TLC as an intermediate. Interestingly, the crystallographic structure of **5**[20] indicates an endodentate conformation, similar to that of cyclam,[24,25] with intramolecular hydrogen bonds linking trans hydrogen atoms H^4, H^{11} and nitrogen atoms N^1, N^8 (Figure 3). Then, it turns out that the second addition preferentially takes place at the trans amine group NH_8 which happens to bear a hydrogen atom not involved in a hydrogen bond, if this solid-state conformation remains favored in the $CHCl_3$ solution.[25]

The change in regioselectivity in the presence of one equivalent of acid may be explained by considering that the second addition step now involves the monoprotonated intermediate **5**·H$^+$. Determination of the site of protonation of compound **5** with PTSA in a chloroform solution has been attempted through an NMR study. COSY and ^1H-^{13}C correlations have allowed the attribution of a number of methylenic signals of **5** and **5**·H$^+$. In addition, complete assignments in the ^1H and ^{13}C NMR spectra of **5**·H$^+$ have been achieved through an HMBC experiment. ^1H NMR spectra and variations of the chemical shifts observed upon successive additions of PTSA to the monosubstituted intermediate **5** are reported in Figure 4 and Figure 5, respectively. Most important variations of chemical shifts are observed for methylenes *c*, *d* and *f* suggesting that the protonation preferentially occurs on nitrogen atom N^4. A previously reported study of the protonation sequence of *N*-2-

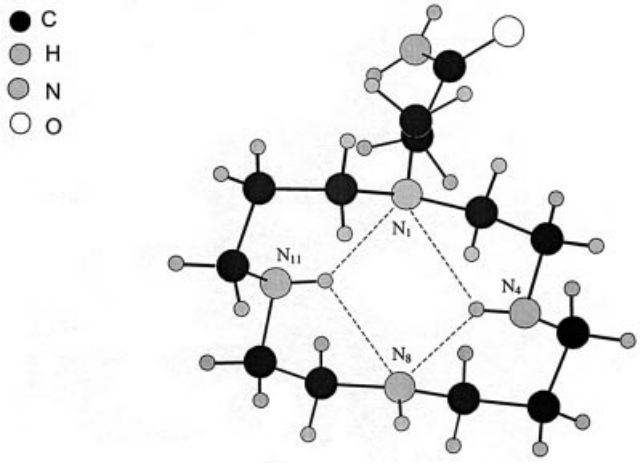


Figure 3. Ball and stick representation of the monoalkylated intermediate **5**. Distances (Å) from X-ray crystallography[20] are as follow: N^1-H^{11} 2.43; N^1-H^4 2.54; N^8-H^{11} 2.46; N^8-H^4 2.28; distances from N^1 or N^4 or N^{11} to H^8 are equal or longer than 2.97 Å

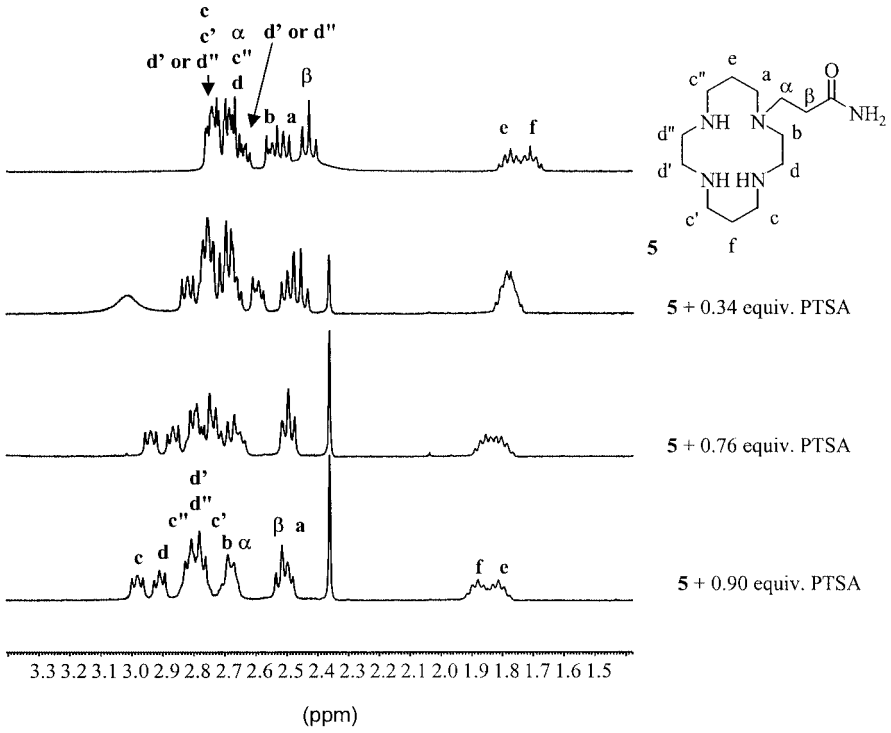


Figure 4. Incremental additions of PTSA to intermediate **5** (^{1}H NMR, $CDCl_3$, 300 MHz)

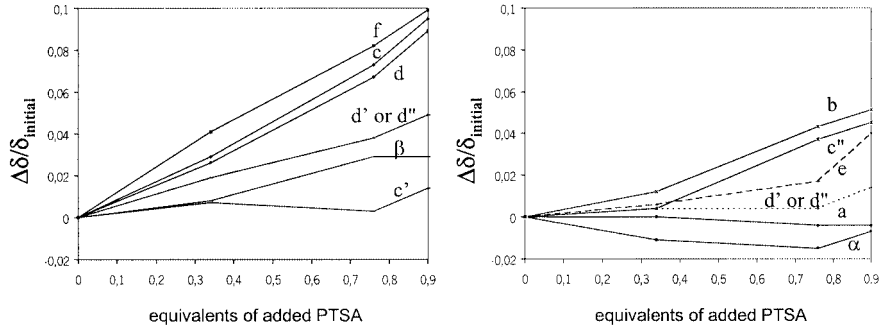


Figure 5. Relative variations of ^{1}H NMR shifts, $\Delta\delta/\delta_{initial}$, as a function of the amount of PTSA added to compound **5**

aminoethylcyclam (scorpiand molecule) has shown that, in water, the first protonation also occurs on N^4.[26]

A similar conclusion can be drawn from the ^{13}C shifts of **5** and **5**·H^+ (Figure 6). Protonation of linear amines results in an upfield shift for carbon nuclei that are in α and β positions relative to the site of the protonation, the greater

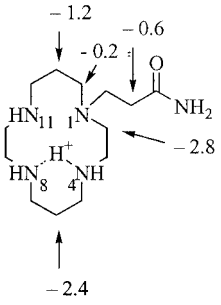


Figure 6. ^{13}C NMR shifts [Δ(δC) in ppm] upon protonation of intermediate **5**. Suggested protonation site in **5**·H^+

shift being observed for the β carbon.[27] The weak variations observed for carbons *a* and β indicate that protonation of **5** does not occur on the substituted nitrogen N^1. On the other hand, the upfield shifts of carbons *b* and *f* are in agreement with a protonation taking place on the lower part of the macrocycle, preferentially on nitrogen N^4 or in dynamic exchange between N^4 and N^8.

Additional NOE and ROESY experiments show connections through space between Hα and H*e*, H*d* and between Hβ and H*d*, H*d*′ in **5**·H^+. These interactions seem to indicate that, in the favored conformation, the ethylcarboxamide substituent lies above the cavity of the macrocycle. Intramolecular hydrogen bonds involving the amide pendant group and the protonated or unprotonated amines N^4 and N^8 may account for such a favored conformation.

Thus, when the addition of cyclam to acrylamide is performed in the presence of acid, the formation of the 1,11-disubstituted regioisomer **2** as a major product might be explained by considering that the second addition takes

place preferentially at the less-hindered free secondary amine site NH_{11} of the protonated intermediate **5**·H^+.

Switching to methanol as a solvent did not significantly modify the previous results obtained in the presence of PTSA but reduced considerably the selectivity of the disubstitution as well as the regioselectivity of the reaction performed without PTSA. With PTSA, in methanol, the overall yield of the disubstitution remained unchanged (78%). Compound **2** was still the major product but the three disubstituted regioisomers were now isolated. The presence of intermediate **5**·H^+ might still explain the observed selectivity in methanol, the proton being tightly associated within the cavity of the macrocycle as mentioned above. On the other hand, a drop in the selectivity was obtained when the reaction was performed in methanol without PTSA. Almost 25% of tetrasubstituted cyclam was now isolated. Disubstitution was not regioselective either since no major regioisomer was obtained among the three isolated disubstituted compounds. The previously reported acceleration of hetero-Michael additions in protic solvents may well account for the observed lack of selectivity in methanol.[28] Thus, in the absence of acid, control of the nucleophilic addition leading to the favored formation of the 1,11-disubstituted compound **1** requires the use of a nonprotic solvent like chloroform.

Conclusion

To the best of our knowledge, this is the first one-step regioselective and tunable synthesis of di-*N*-substituted tetraazamacrocycles. Each regioisomer has been isolated and characterized. Rationalization of the observed regioselectivity is suggested on the basis that the stepwise reaction involves either a free or a monoprotonated monoalkylated intermediate. The mild reaction conditions should allow the introduction of a variety of pendant arms on the cyclam moiety and the position of the two alkyl substituents might be controlled depending upon the presence or absence of an acid in the reaction medium.

Experimental Section

General Remarks: ^1H, ^{13}C, and 2D (COSY, ^1H-^{13}C, and HMBC correlations, ROESY) spectra have been recorded at 300−75 MHz or 500−125 MHz. Mass spectra were obtained on a MS-ENGINE (HP5989B) by direct introduction. Electrospray was used in the positive mode and the samples were diluted in H_2O: MeOH (20:80) + 1% CH_3COOH. TLC analysis was performed on silica plates (Merck $60F_{254}$) with $Cu(NO_3)_2$·$3H_2O$ (0.2% in absolute ethanol) or ninhidrin (0.2% in absolute ethanol) as a revelator. Column chromatography was carried out with silica gel GEDURAN SI60 from Merck. Ammonia in the eluent system $CHCl_3$/MeOH/NH_4OH was used as 32% in water. Acrylamide was commercially available.

Compounds 1 and 2: Cyclam (200 mg, 1 mmol) was placed in a 10-mL round-bottomed flask and acrylamide (142 mg, 2 mmol) and chloroform (4 mL) were added. 2,4-di-*tert*-butyl phenol (2 mg) was added to the reaction mixture which was stirred at room temperature (in the absence of light) for four days. The product was chromatographed through silica gel using $CHCl_3$/CH_3OH/NH_4OH (8:4.5:1) as the eluent. Compounds **1** and **2** were obtained as colorless oils in 43 and 18% yields, respectively.

Compounds 2 and 3: These were prepared using the procedure described above, using cyclam (200 mg, 1 mmol), acrylamide (142 mg, 2 mmol) and *p*-toluenesulfonic acid (190 mg, 1 mmol) in chloroform (4 mL). Compounds **2** and **3** were isolated as colorless oils in 50 and 30% yields, respectively, after column chromatography on silica gel using $CHCl_3$/CH_3OH/NH_4OH (8:4.5:1) as the eluent.

Supporting Information (NMR spectra of compounds **1**, **2**, **3**, and **5**·H^+) for this article is available (see also footnote on the first page of this article).

Compound 1: R_f(**1**) = 0.7 ($CHCl_3$/CH_3OH/NH_4OH, 2:2:1). ^1H NMR (CD_3OD/$CDCl_3$, 7:1): δ = 1.78 (m, 4 H, e), 2.37 (t, *J* = 7.2 Hz, 4 H, β), 2.53−2.57 (m, 8 H, a, b), 2.69−2.80 (m, 12 H, c, d, α) ppm. ^{13}C NMR (CD_3OD/$CDCl_3$, 7:1): δ = 26.12 (e), 32.68 (β), 47.89 (d), 50.20 and 50.44 (c, α), 53.04 and 53.52 (a, b), 177.53 (CO) ppm. MS (relative abundance): *m*/*z* (%) = 343 [M + H^+] (100). ^{13}C NMR peaks were attributed according to the ^1H-^{13}C correlation.

Compound 2: R_f(**2**) = 0.5 ($CHCl_3$/CH_3OH/NH_4OH, 2:2:1). ^1H NMR (CD_3OD/$CDCl_3$, 7:1): δ = 1.64 (m, 2 H, e), 1.77 (m, 2 H, f), 2.33 (t, *J* = 6.6 Hz, 4 H, β), 2.44 (t, *J* = 6.57 Hz, 4 H, a), 2.52−2.56 (m, 4 H, b), 2.69 (t, *J* = 6.5 Hz, 4 H, α), 2.71−2.72 (m, 8 H, c, d) ppm. ^{13}C NMR (CD_3OD/$CDCl_3$, 7:1): δ = 26.94 (e), 27.54 (f), 33.55 (β), 46.45 and 47.26 (c, d), 50.44 (α), 50.93 (a), 53.14 (b), 177.66 (CO) ppm. MS (relative abundance): *m*/*z* (%) = 102 (100), 149 (84), 167 (36), 343 [M + H^+] (33).

Compound 3: R_f(**3**) = 0.6 ($CHCl_3$/CH_3OH/NH_4OH, 2:2:1). ^1H NMR (CD_3OD/$CDCl_3$, 7:1): δ = 1.79 (m, 4 H, e), 2.40 (t, *J* = 6.8 Hz, 4 H, β), 2.54 (t, *J* = 5.9 Hz, 4 H, a), 2.56 (s, 4 H, b), 2.73 (t, *J* = 6.9 Hz, 4 H, α), 2.77 (t, *J* = 5.5 Hz, 4 H, c), 2.97 (s, 4 H, d) ppm. ^{13}C NMR (CD_3OD/$CDCl_3$, 7:1): δ = 25.48 (e), 32.43 (β), 46.40 (d), 46.87 (c), 50.02 (α), 51.86 and 52.20 (a, b), 177.55 (CO) ppm. MS (relative abundance): *m*/*z* (%) = 149 (100), 343 [M + H^+] (70).

Compound 4: Compound **2** (20 mg) was stirred in CH_2Cl_2 (5 mL) and CH_3OH (0.3 mL). After concentrating the reaction mixture to an oil, the mass spectrum was recorded.

After stirring the reaction mixture for five days: MS (relative abundance): *m*/*z* (%) = 343 [**2**·H^+] (100), 355 [**4**·H^+] (14).

After stirring for one month: MS (relative abundance): *m*/*z* (%) = 343 [**2**·H^+] (17), 355 [**4**·H^+] (100).

Compound **5** has been synthesized and characterized previously.[20] The following NMR spectra of compound **5**·H^+ were recorded starting from **5** (5.7 mg) and PTSA (2.7 mg) in $CDCl_3$ (0.75 mL).

Compound 5·0.9 PTSA: ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.79 (m, 2 H, e), 1.87 (m, 2 H, f), 2.36 (s, 3 H, CH_3), 2.47 (m, 2 H, a), 2.50 (m, 2 H, β), 2.63 (m, 2 H, α), 2.67 (m, 2 H, b), 2.78, 2.79, 2.80, 2.81 (m, 8 H, c′, d′ or d′′, c′′, d′′ or d′, respectively), 2.92 (t, *J* = 5.1 Hz, 2 H, d), 2.98 (t, *J* = 5.3 Hz, 2 H, c), 7.19 (d, *J* = 8.1 Hz, 2 H, H_{PTSA}), 7.77 (d, *J* = 8.1 Hz, 2 H, H_{PTSA}) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): 21.31 (CH_3, APTS), 23.84 (e), 24.75 (f), 32.30 (β), 45.06 (d′ or d′′), 45.43 (d), 46.51 (c′ and d′ or d′′), 47.14 (c′′), 48.52 (α), 49.22 (c), 50.35 (b), 52.06 (a); 125.77, 128.87, 140.13, 142.25, 174.97 (aromatic, PTSA) ppm.

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