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Samarium-Promoted Asymmetric Aldol–Tishchenko Reaction: Synthesis of Amino Acid-Derived 4-Amino-1,3-diols

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Abstract: A samarium-mediated novel synthesis of enantiopure 4-amino-1,3-diols is carried out through a samarium-promoted aldol–Tishchenko reaction starting from chiral α′-amino-α-chloro ketones (derived from natural α-amino acids) and aldehydes. The process takes place with moderate levels of stereoselectivity and in high yields. A mechanism is proposed to explain these results while the absolute configuration and structure of the aldol–Tishchenko adducts were established by X-ray analysis. This method has also been utilized for the synthesis of enigmols, 1-deoxysphingoid base analogues.

Keywords: aldol reaction; amino acids; enolates; samarium; Tishchenko reaction

The 4-amino-1,3-diol moiety belongs to a family of compounds – enigmols – which are known as 1-deoxysphingoid base analogues; they have demonstrated promising activity against prostate[1] and colon[2] cancer. These compounds are generally identified as a potential new class of anticancer principles.[3]

The aldol–Tishchenko reaction (aldol/Tishchenko tandem process)[4] allows the conversion of aldehydes and ketones into 1,3-dihydroxy compounds. This reaction has been previously reported employing different catalysts such as samarium,[5] yttrium,[6] lithium,[7] titanium,[8] ytterbium,[9] zirconium,[10] aluminium,[11] and lanthanum[12] species.

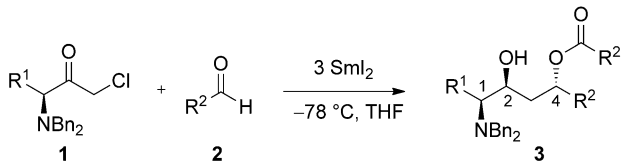
One of the most frequently used strategies to prepare enantiopure compounds is based on the use of optically active natural products as starting materials. Thus, α-amino acids have been one of the most utilized sources of chiral compounds in synthetic organic chemistry. Enantiopure α-amino ketones are easily obtained from readily available natural α-amino acids and they have been extensively utilized as building blocks in organic synthesis. In this sense, our group has previously described the synthesis of chiral α′-amino α-chloro ketones **1** by treatment of easily available α-amino esters with *in situ* generated chloromethyllithium.[13] We have also described some synthetic applications of these α-amino chloromethyl ketones,[14] such as the preparation of enantiopure *threo*-aminoalkylepoxides,[15] 3-azetidinols,[16] amino epihalohydrins,[17] α′-amino-α,β-epoxy ketones,[18] aminoaziridines (from their ketimine derivatives),[19] γ-amino ester azetidinium salts and epoxy esters,[20] amino-γ-butyrolactones and butenolides,[21] *pseudo*-C_2-symmetric diepoxides,[22] and chiral trisubstituted piperidines.[23]

In recent years samarium diiodide has rapidly become an important reagent in organic chemistry because of its versatility in one- and two-electron transfer reactions. Thus, since the pioneering studies of Kagan,[24] many synthetic applications of this reagent were reported from our group and others.[25]

Encouraged by the pharmacological interest in enigmols,[1,2] and motivated by our studies on the synthetic applications of α′-amino-α-chloro ketones and the development of new applications of samarium diiodide in organic synthesis, in this communication we report the employment of α-amino chloromethyl ketones and aldehydes as starting materials for the synthesis of enigmol targets through an aldol–Tishchenko reaction, this process being promoted by samarium diiodide.

Our first attempts were performed using the *N,N*-dibenzylamino chloromethyl ketone derived from L-alanine **1a** and *n*-octanal **2a**. After searching for the optimum conditions for this reaction, 1.0 equiv. of **1a**

Table 1. Synthesis of aldol–Tishchenko adducts **3**.



Entry	3	R^1	R^2	*dr*[a] 1,2-*syn*/1,2-*anti*	Yield [%][b]
1	**3a**	Me	*n*-C_7H_{15}	2.5/1	80
2	**3b**	Me	*i*-Bu	2.5/1	81
3	**3c**	Me	*c*-C_6H_{11}	3/1	80
4	**3d**	*i*-Bu	*n*-C_7H_{15}	3/1	91
5	**3e**	*i*-Bu	*i*-Bu	3/1	90
6	**3f**	*i*-Bu	*c*-C_6H_{11}	3.5/1	88
7	**3g**	Bn	*n*-C_7H_{15}	1.7/1	79
8	**3h**	Bn	*i*-Bu	1.5/1	90
9	**3i**	Bn	*c*-C_6H_{11}	2.5/1	85

[a] Diastereoisomeric ratio (*dr*) 1,2-*syn*/1,2-*anti* was determined by 300 MHz ^{1}H NMR analysis of crude products **3**. Stereogenic centers 2, and 4 are always present in a relative *trans*-configuration.

[b] Isolated yields of analytically pure compounds **3**.

and 2.5 equiv. of **2a** in THF were added dropwise to a solution of SmI_2 (3.0 equiv., 0.1 M in THF) at −78 °C. The reaction mixture was stirred for one additional hour at −78 °C. The solution was finally allowed to warm to room temperature and poured into a mixture of saturated aqueous $Na_2S_2O_3$/$NaHCO_3$ and washed with brine. The aldol–Tishchenko adduct **3a** was isolated in 80% yield and in a diastereoisomeric ratio 2.5/1 (Table 1).

Using these conditions, other aliphatic aldehydes (branched **2b** and cyclic **2c**) were employed. In all cases aldol–Tishchenko adducts **3a–c** were obtained in high yields with moderate stereoselectivities. When the reaction was carried out with aromatic aldehydes, products derived from a pinacol coupling reaction were obtained instead, due to the reductive coupling reaction of aromatic aldehydes in the presence of samarium diiodide.[26]

Under the above-mentioned reaction conditions, 1-aminoalkyl chloromethyl ketones derived from L-leucine **1b** and L-phenylalanine **1c** also afforded with moderate stereoselectivities the corresponding aldol–Tishchenko adducts in high yields ranging between 79–91% (Table 1). The degree of stereoselectivity was only moderately affected by the steric demand of R^2 on aldehydes **2**. So, the stereoselectivity observed in the aldol–Tishchenko reaction was slightly higher in the case of cyclohexanecarbaldehyde **2c,** and similar for *n*-octanal **2a** or 3-methylbutanal **2b** (Table 1). The structure of aldol–Tishchenko adducts **3** was assigned based on ^{1}H, ^{13}C, HMBC and HSQC NMR experiments. The diastereoselectivity of the reaction was established by ^{1}H NMR spectroscopy experiments on crude reaction mixtures. The analyses of the spectra showed that all aldol–Tishchenko adducts **3** were isolated with a diastereoisomeric ratio ranging between 1.5/1 to 3.5/1. These *dr* values should be analyzed taking into account that there are three stereogenic centers in aldol–Tishchenko adducts **3**, two of them being generated during the reaction. Thus, given that the stereochemistry of the *CHN* carbon center is fixed on the starting material, these results indicated that the moderate stereoselectivity observed is a consequence of the aldol process. This fact will be conveniently explained in the mechanistic proposal.

It is noteworthy that, although moderate stereoselectivity was observed in products **3a–i**, major and minor stereoisomers were separately isolated after chromatography (hexane/EtOAc = 10/1). The absolute configuration of the major stereoisomer of compound **3i** was unambiguously confirmed by a single-crystal X-ray diffraction study (Figure 1) and was therefore assigned as **3i**-(1*S*,3*S*,4*S*).[27] The absolute configurations of other aldol–Tishchenko adducts **3** were assigned by analogy and also confirmed the absence of racemization by HPLC chiral analysis (see below).

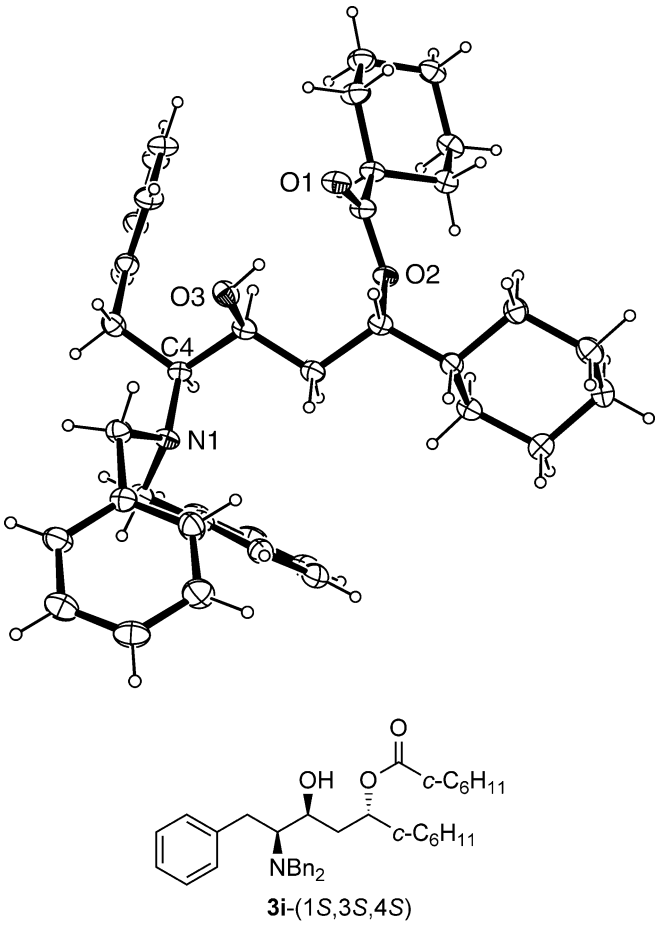
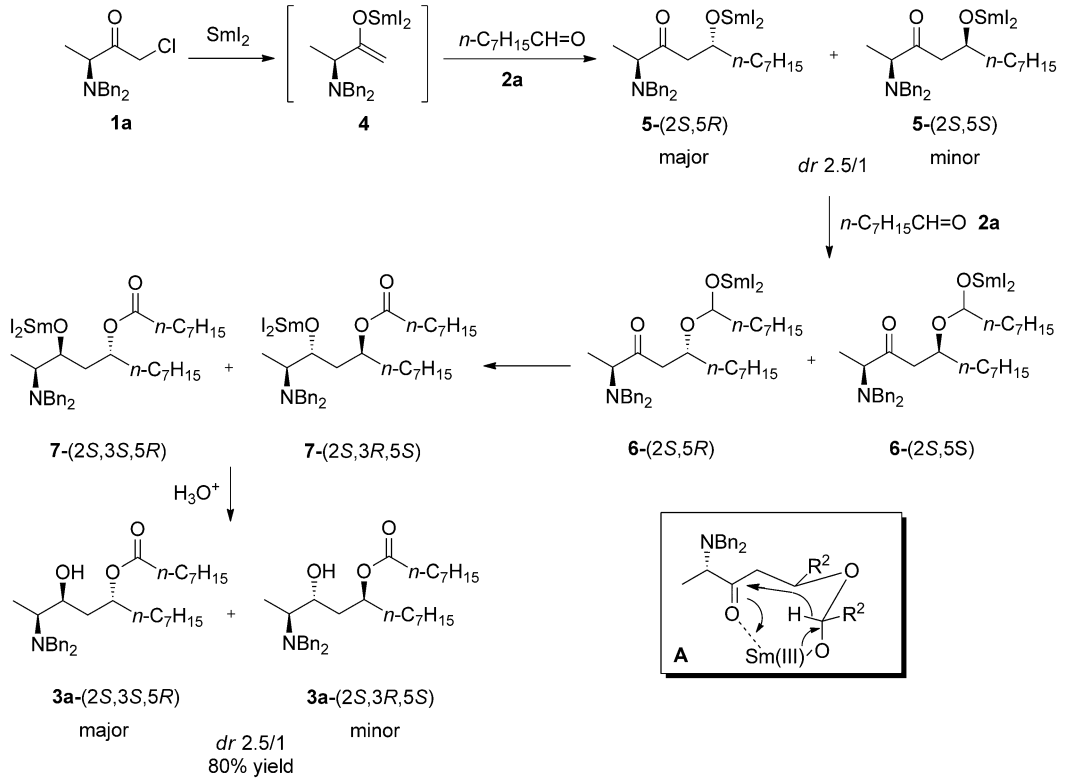


Figure 1. ORTEP diagram for **3i**-(1*S*,3*S*,4*S*).



Scheme 1. Mechanistic proposal for the synthesis of **3a** from **1a**.

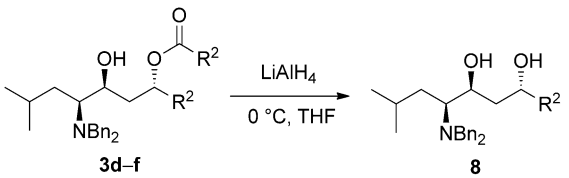
A plausible mechanism for this samarium-promoted aldol-Tishchenko reaction involves an initial metalation of the C–Cl bond on aminoalkyl chloromethyl ketone **1a** to afford samarium enolate **4**. The addition of this samarium enolate to the corresponding aldehyde (**2a**) would generate stereoisomeric samarium β-alkoxy ketones **5** in which the samarium(III) atom would act as a Lewis acid, due to its high oxophilicity,[28] to coordinate with one molecule of the aldehyde, and to facilitate the addition of a second equivalent of aldehyde generating hemiacetal intermediates **6**. These species **6** would undergo an intramolecular 1,5-hydride shift that would result in the production of samarium alcoholates **7** which, after hydrolysis, would finally afford the corresponding aldol–Tishchenko adducts **3a**-(2*S*,3*S*,5*R*) and **3a**-(2*S*,3*R*,5*S*) in 80% yield (see Experimental Section).

The moderate stereoselectivity observed in adducts **3** could be explained as a consequence of the aldol process rather than the Tishchenko reaction, since it has been previously reported that for the samarium-catalyzed intramolecular Tishchenko reduction of β-hydroxy ketones, the transformation affords the corresponding *anti* diol monoesters in high yield and with excellent levels of stereochemical control.[5d] These high levels of stereochemical control are explained using a six-membered transition state (depicted as **A** in Scheme 1) and it is similar to that proposed by Evans[5d] and Schreiber.[5c] for the *anti* selective samarium-catalyzed Tishchenko reduction of β-hydroxy ketones.

To illustrate some synthetic possibilities of this method, aldol–Tishchenko adducts **3d–f** (major stereoisomers) were transformed into the corresponding diols **8a–c** by reaction with $LiAlH_4$, in THF, at 0 °C for 6 h. After these reaction conditions, amino diols **8** were isolated without any loss of diastereoisomeric purity and in high yields (Table 2).

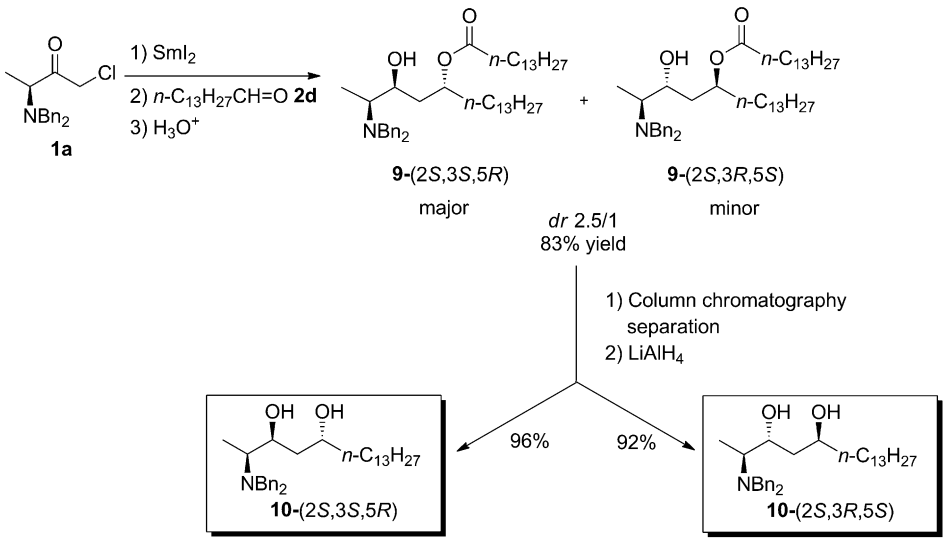
The enantiomeric purity of compounds **8** was determined by chiral HPLC chromatography of **8d** showing an enantiomeric excess (*ee*) >98%. A racemic mix-

Table 2. Synthesis of enantiopure amino diols **8**.



Entry	**8**	R^1	R^2	Yield [%][a]
1	**8a**	*i*-Bu	n-C_7H_{15}	91
2	**8b**	*i*-Bu	*i*-Bu	92
3	**8c**	*i*-Bu	c-C_6H_{11}	95
4	**8d**	$PhCH_2$	*i*-Bu	94

[a] Isolated yield of pure compounds **8** after column chromatography based on compounds **3**.



Scheme 2. Synthesis of **10**-(2*S*,3*S*,5*R*) and **10**-(2*S*,3*R*,5*S*).

ture of **8d** was prepared from racemic phenylalanine to exclude the possibility of coelution of both enantiomers in HPLC.[29]

As it has been previously indicated, enigmols are interesting compounds due to their pharmacological utilities. In this sense, our next efforts were directed towards the synthesis of enigmol analogues using this samarium-promoted aldol–Tishchenko methodology. So, *N,N*-dibenzylamino chloromethyl ketone derived from L-alanine **1a** and *n*-tetradecanal **2d** was added dropwise to a solution of SmI_2 (3.0 equiv., 0.1 M in THF) at −78 °C (Scheme 2). After stirring for one hour the solution was finally allowed to warm to room temperature. After work-up adducts **9**-(2*S*,3*S*,5*R*) and **9**-(2*S*,3*R*,5*S*) were isolated in 83% yield and in a diastereoisomeric ratio 2.5/1. Column chromatography separation and further reduction of both stereoisomers allowed the synthesis of enigmol analogues **10**-(2*S*,3*S*,5*R*) and **10**-(2*S*,3*R*,5*S*) which were fully characterized and, in the case of compound **10**-(2*S*,3*R*,5*S*), compared with the data previously reported in the literature for the same compound.[1b]

In conclusion, we have a described new samarium-mediated aldol–Tishchenko protocol for the synthesis of 4-amino-1,3-diol targets starting from chiral α′-amino-α-chloro ketones (derived from natural α-amino acids) and aldehydes. This process took place with moderate levels of stereoselectivity and the diasteroisomers were easily separated by column chromatography. The absolute configuration and structure of aldol-Tishchenko adducts have been well established by X-ray analysis. This method has also been utilized for the stereoselective preparation of enigmol analogues.

Experimental Section

Synthesis of (2*S*,3*S*,5*R*)/(2*S*,3*R*,5*S*)-2-Dibenzylamino-3-hydroxydodecan-5-yl Octanoate (3a)

A 0.1 M solution of samarium diiodide in tetrahydrofuran (3 equiv., 1.5 mmol, 15 mL) was prepared and cooled to −78 °C. Then, a solution of the (*S*)-3-dibenzylamino-1-chlorobutan-2-one **1a** (1 equiv., 0.5 mmol, 151 mg) and octanal (2.5 equiv., 1.25 mmol, 0.2 mL) in 25 mL THF was added dropwise to the SmI_2 solution. The reaction mixture was stirred for an additional 1 h at −78 °C. Then the solution was allowed to warm to room temperature, air was bubbled through, and it was finally poured into a mixture of saturated aqueous $Na_2S_2O_3$/$NaHCO_3$ and brine. The aqueous layer was extracted with Et_2O (2×20 mL), and the combined organic layers washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (hexane/AcOEt = 10:1), to afford pure **3a**-(2*S*,3*S*,5*R*), and **3a**-(2*S*,3*R*,5*S*) as major an minor stereoisomers, respectively.

Major stereoisomer 3a-(2*S*,3*S*,5*R*): yellow oil; $[\alpha]_D^{20}$: −1.6 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.22 (m, 10H), 5.22–5.13 (m, 1H), 3.85 (d, *J* = 13.3 Hz, 2H), 3.49 (t, *J* = 9.3 Hz, 1H), 3.34 (d, *J* = 13.3 Hz, 2H), 2.61–2.50 (m, 1H), 2.30 (t, *J* = 7.3 Hz, 2H), 1.69–1.24 (m, 24H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.92–0.84 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2 (C), 138.8 (2 × C), 128.9 (4 × CH), 128.4 (4 × CH), 127.1 (2 × CH), 71.6 (CH), 67.5 (CH), 58.5 (CH), 53.3 (2×CH_2), 38.9 (CH_2), 35.0 (CH_2), 34.6 (CH_2), 31.7 (2×CH_2), 29.4 (CH_2), 29.0 (2×CH_2), 28.9 (CH_2), 25.1 (2×CH_2), 22.5 (2×CH_2), 14.0 (2×CH_3), 8.0 (CH_3); MS (ESI$^+$-TOF): *m/z* (%) = 565 (16), 524 ([M+H]$^+$, 100), 483 (73), 338 (15); HR-MS: *m/z* = 524.4102, calcd. for $C_{34}H_{54}NO_3$ [M+H]$^+$: 524.4098; IR (neat): ν = 2927, 2856, 1732 cm^{-1}; R_f = 0.48 (hexane/EtOAc = 10:1).

Minor stereoisomer 3a-(2*S*,3*R*,5*S*): yellow oil; $[\alpha]_D^{20}$: −1.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.06 (m, 10H), 5.00–4.88 (m, 1H), 3.62 (d, *J* = 13.6 Hz, 2H),

3.46–3.31 (m, 1H), 3.33 (d, $J=13.7$ Hz, 2H), 3.05 (br s, 1H), 2.52 (m, $J=6.6$ Hz, 1H), 2.27–2.17 (m, 2H), 1.50–1.13 (m, 24H), 1.05 (d, $J=6.6$ Hz, 3H), 0.82–0.76 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=175.2$ (C), 140.0 (2×C), 128.7 (4×CH), 128.1 (4×CH), 126.7 (2×CH), 71.7 (CH), 69.0 (CH), 57.0 (CH), 54.2 (2×CH_2), 40.3 (CH_2), 34.9 (CH_2), 34.5 (CH_2), 31.6 (2×CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 25.4 (CH_2), 25.1 (CH_2), 22.5 (CH_2), 14.0 (CH_2), 8.5 (CH_3); MS (ESI$^+$-TOF): m/z (%)=524 ([M+H]$^+$, 100); HR-MS: $m/z=524.4115$, calcd. for $C_{34}H_{54}NO_3$ [M+H]$^+$: 524.4104; $R_f=0.42$ (hexane/EtOAc=10:1)

Synthesis of (4*S*,5*S*,7*R*)-4-(Dibenzylamino)-2-methyltetradecane-5,7-diol (8a)

The corresponding ester **3a-**(2*S*,3*S*,5*R*) (1 equiv., 0.2 mmol, 105 mg) was dissolved in THF (2 mL) and cooled to 0 °C, Then a 1.0 M solution of $LiAlH_4$ in diethyl ether (1.1 equiv., 0.22 mmol, 0.22 mL) was added dropwise and the reaction mixture was stirred for 6 h. After that, the solution was quenched with ice-water and filtered through a Celite® pad. The aqueous layer was extracted with Et_2O (2×5 mL), and the combined organic layers dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (hexane/AcOEt=5:1), affording pure amino diol **8a**; yield: 91%; $[\alpha]_D^{20}$: +16.4 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.42$–7.11 (m, 10H), 4.72 (br s, 1H), 3.79 (d, $J=13.4$ Hz, 2H), 3.65 (dq, $J=8.5$, 3.8 Hz, 2H), 3.37 (d, $J=13.4$ Hz, 2H), 2.91 (br s, 1H), 2.54 (dt, $J=9.8$, 5.7 Hz, 1H), 1.76–1.02 (m, 17H), 0.88 (d, $J=6.4$ Hz, 6H), 0.85–0.76 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=138.9$ (2×C), 128.9 (4×CH), 128.5 (4×CH), 127.3 (2×CH), 68.8 (2×CH), 60.3 (CH), 53.8 (2×CH_2), 39.2 (CH_2), 37.3 (CH_2), 35.7 (CH_2), 31.8 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 26.6 (CH), 25.7 (CH_2), 23.2 (CH_3), 23.0 (CH_3), 22.6 (CH_2), 14.0 (CH_3); MS (ESI-TOF): m/z (%)=440 ([M+H]$^+$, 100), 422 ([M$^+-H_2O$], 20); HR-MS: $m/z=440.3533$, calcd. for $C_{29}H_{46}NO_2$ [M+H]$^+$: 440.3529; $R_f=0.23$ (hexane/EtOAc=5:1)

Supporting Information

Characterization data as well as ^{1}H/^{13}C NMR spectra of all new compounds **3**, **8** and **10** are available in the Supporting Information.

Acknowledgements

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