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An expeditious synthesis of bistratamide H using a new fluorous protecting group

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Abstract—A total synthesis of bistratamide H has been achieved using a new 'highly' fluorous amino protecting group, tris(perfluorodecyl)silylethoxylcarbonyl (^{F}Teoc) group. The synthetic intermediates were easily isolated by liquid–liquid extraction with fluorous solvent. The fluorous protecting group was demonstrated to be recycled.
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Bistratamides and didmolamides were isolated from ascidians *Lissoclinum bistratum* and *Didemnum molle* in the southern Philippines and in Madagascar, respectively.[1] They are cyclic tri- or tetra-peptides of amino acids that include thiazole, oxazole and oxazoline (Fig. 1). The unique macrolactam structures and their bioactivities such as moderate cytotoxic activity, anti-microbial and anti-drug resistance properties have attracted synthetic organic chemists' interest. Among them, Kelly's and Shin's groups have recently synthesized some of bistratamides independently according to their own methodologies of thiazole amino acid synthesis. Kelly described in his reports that 'Construction of the thiazoles in these macrolactams is central to their total synthesis' and found a facile and efficient biomimetic synthesis of thiazoles accomplished by treating N-acylated cysteine with bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate followed by oxidation of the thiazolines employing activated MnO_2.[2] Shin and his co-workers have synthesized bistratamide G in a high total yield by a modified Hantzsch's method using thioamide and bromoacyl derivatives of an oxazole amino acid as intermediates, which were prepared from dehydropeptides. Coupling the thioamide and bromoacyl moieties of the intermediates led to the thiazole amino acid part of bistratamide G.[3]

These interesting works prompted us to employ fluorous technologies for an expeditious synthesis of bistratamide H due to the following reasons. Firstly, Kelly's group also synthesized didmolamines A and B by a solid phase assembly of thiazole-containing amino acids.[4] However the amino acids were prepared by the above biomimetic synthetic methods without using the solid support. Secondly, the modified Hantzsch's method used by Shin's group includes thiocarbonylation of α-amino acid amide with Lawesson's reagent. In the reaction, it is very difficult to separate the products from unbearably bad smelling by-products by silica gel column chromatography. Partial racemization of the products during the reactions is another problem of this method.

Unlike Kelly's solid support synthesis, fluorous protecting groups can be used from the beginning of the modified Hantzsch's route for protecting amino groups of α-amino acids. If fluorine atom contents of intermediates of the route are enough high, the fluorous intermediates can be separated clearly from organic by-products including the bad smelling ones by liquid–liquid extraction with fluorous and organic solvents.[5] Optimization of the reaction conditions is expected to be accomplished by checking the enantiomeric purity of the fluorous intermediates by HPLC with a chiral column to avoid the racemization of the intermediates. An excellent method using fluorous supports such as HfBz and HfBn has already been reported by Inazu and his co-workers for oligopeptide and oligosaccharide syntheses.[6] However, we wanted to synthesize bistratamide H by using fluorous protecting groups in order to apply our method also to a fluorous mixture synthesis.[7]

In an early stage of this work, we confirmed that Curran's fluorous Boc-protecting group[8] and Bannwarth

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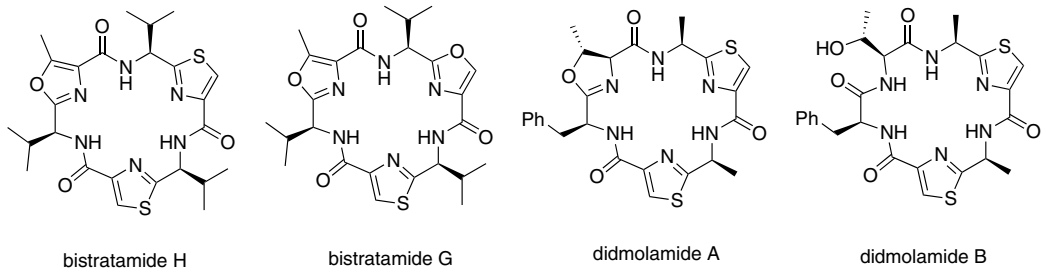


Figure 1. Bistratamide and didmolamide macrolactams.

type heavy fluorous Cbz-protecting group[9] worked well for valine to give the corresponding thiazole amino acid derivative in good yield by a modified Hantzsch's method. However, the light fluorous Boc-protecting group is more practical for small scale synthesis and the heavy fluorous Cbz-protecting group was very unreactive to hydrogenation over palladium on charcoal because of inactivation of the catalyst by sulfur atom of thiazole ring. Therefore we tried to prepare a new type of protecting group suitable for the modified Hantzsch's method and finally reached 2-[tri(perfluorodecyl)-silyl]ethoxycarbonyl (^{F}Teoc) group, a fluorous version of 2-(trimethylsilyl)ethoxycarbonyl group.[10] The fluorous protecting group has a simple structure and thus high fluorine atom content and can be deprotected by tetrabutylammonium fluoride (TBAF). Fluorous protecting agent, 2-[tris(perfluorodecyl)silyl]ethoxy-carbonyl-*O*-succimide (^{F}Teoc-OSu) was prepared as shown in Scheme 1.

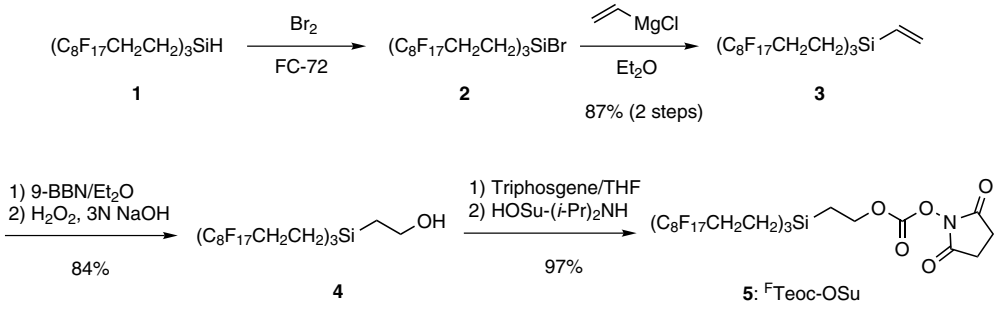
Fluorous hydrosilane **1** was reacted with bromine in FC-72 (perfluorohexane) to give the corresponding silylbromide **2** and then the silylbromide was reacted with vinyl magnesium chloride to give vinylsilane **3** in 87% yield via the two steps. The vinylsilane **3** was reacted with 9-borabicyclo[3,3,1]nonane (9-BBN) and then treated with hydrogen peroxide to give fluorous silylethanol **4** in 84% yield.[11] The silylethanol **4** was treated with triphosgene and then reacted with *N*-hydroxysuccimide (HOSu). After purification of the crude product by silica gel column chromatography, the fluorous protecting agent ^{F}Teoc-OSu **5** was obtained in 97% yield as white solid. The overall yield from the hydrosilane **1** was about 70%.

By using ^{F}Teoc-OSu **5**, we next examined a synthesis of thiazole amino acid derivative from valine by the modified Hantzsch's method (Scheme 2).

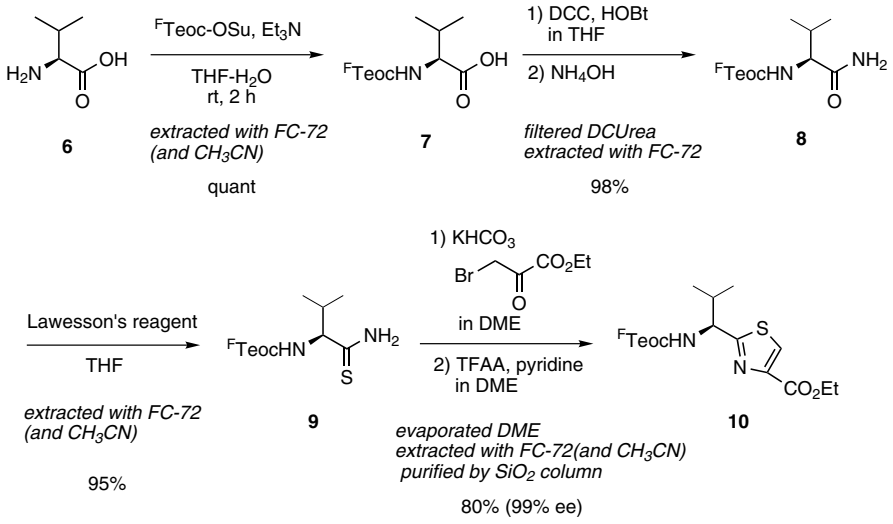
Valine **6** was reacted with ^{F}Teoc-OSu **5** in the presence of triethylamine in aqueous THF. After the reaction, the reaction mixture was acidified and then extracted with FC-72 and acetonitrile. Concentration of the FC-72 layer gave *N*-^{F}Teoc-valine (^{F}Teoc-Val-OH; **7**) in quantitative yield. ^{F}Teoc-Val-OH **7** was reacted with DCC and 1-hydroxybenzotriazle (HOBt) in THF and then treated with an aqueous ammonia solution. The reaction mixture was filtered to remove DCU and then the filtrate was extracted with FC-72. Concentration of the FC-72 layer gave *N*-^{F}Teoc-Val-amide **8** in 98% yield. The amide **8** was reacted with Lawesson's reagent in THF and then the reaction mixture was extracted with FC-72 and acetonitrile. The bad smelling by-products and the reagent were completely partitioned into an organic layer. Therefore, *N*-^{F}Teoc-Val-thioamide **9** obtained from the FC-72 layer was almost odourless. The thioamide **9** was reacted with excess amount of ethyl bromopyruvate in DME and then treated with trifluoroacetic anhydride (TFAA) and pyridine. After evaporating DME, the reaction mixture was extracted with FC-72 and acetonitrile and the crude product obtained from FC-72 layer was purified by silica gel column chromatography to provide *N*-^{F}Teoc-thiazole amino acid ester (^{F}Teoc-Val-Thz-OEt; **10**) in 80% yield as waxy solid. The overall yield from valine was about 74%. Enantiomeric purity of the product **10** was determined to be higher than 99% ee by HPLC with a chiral column, DAICEL CHIRALCEL OD-H.

Another component of bistratamide H, oxazole amino acid methyl ester (H-Val-MeOxz-OMe; **14**) was prepared from ^{F}Teoc-Val-OH **7** via four step reactions (Scheme 3).

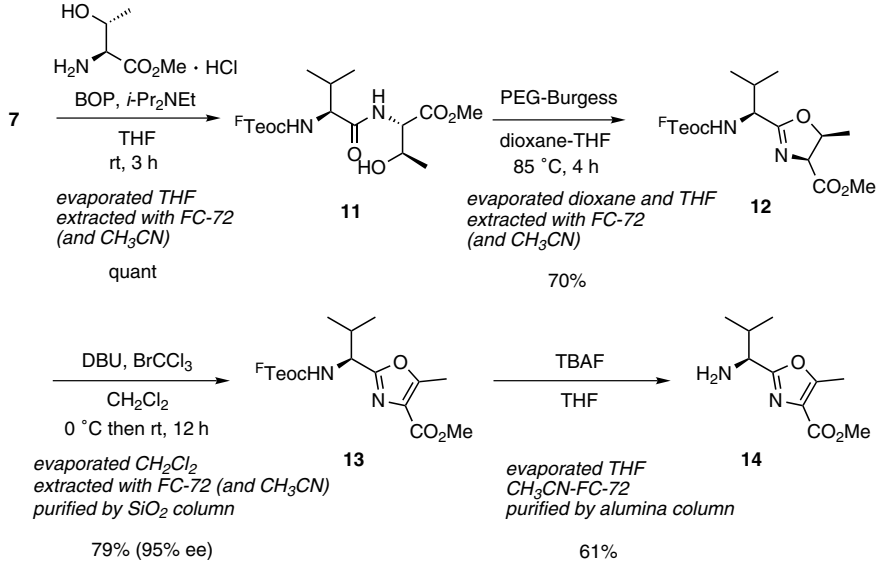
^{F}Teoc-Val-OH **7** was coupled with threonine using benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexa-



Scheme 1. Preparation of fluorous protecting agent ^{F}Teoc-OSu.



Scheme 2. Preparation on *N*-^{F}Teoc-thiazole amino acid ester, ^{F}Teoc-Val-Thz-OEt, from valine.

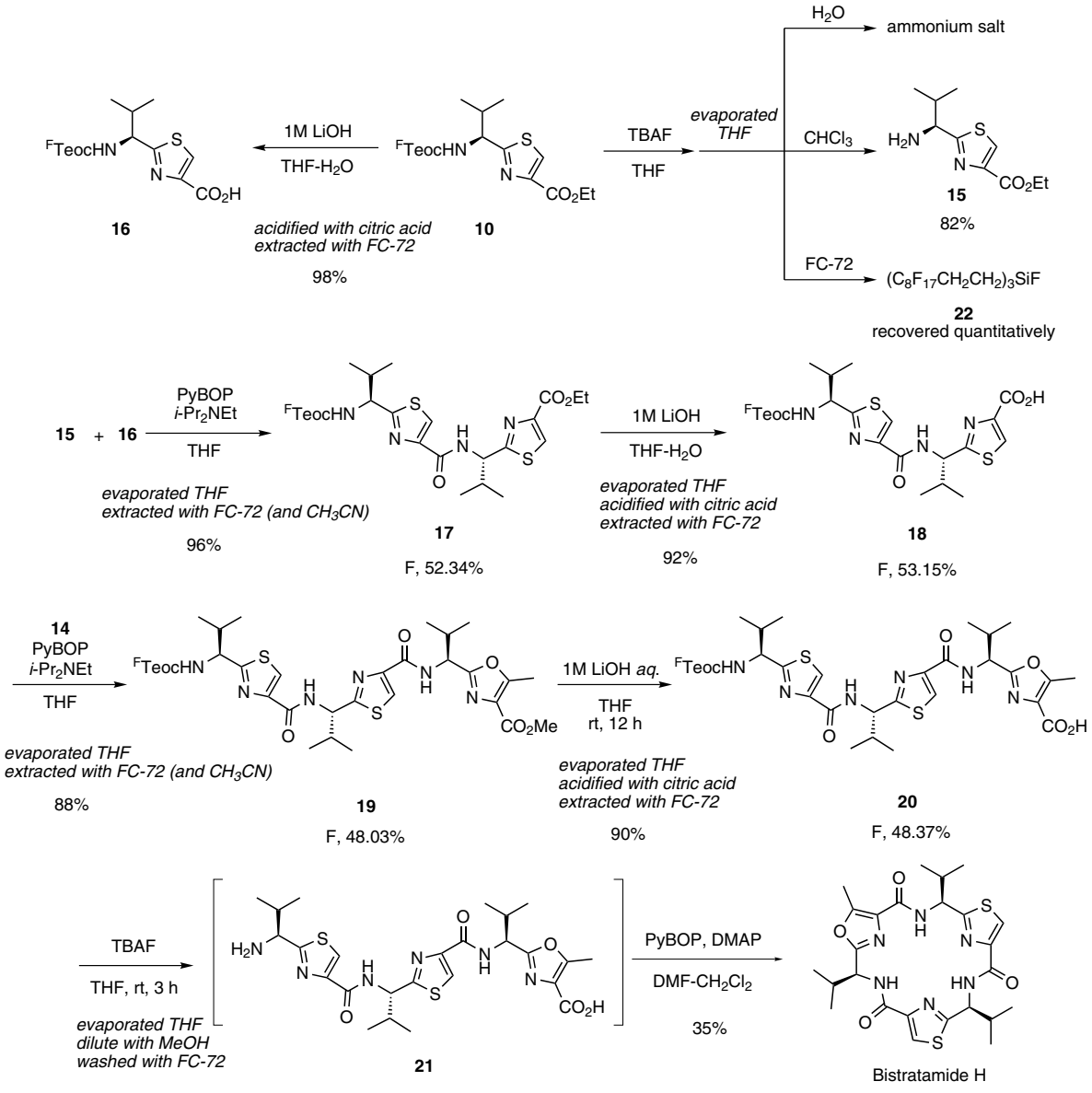


Scheme 3. Preparation of methyloxazole amino acid methyl ester, H-Val-MeOxz-OMe, from *N*-^{F}Teoc-valine.

fluorophosphate (BOP) and *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt) in THF. Evaporation of THF, extraction of the residue with FC-72 and acetonitrile and concentration of the FC-72 layer gave ^{F}Teoc-Val-Thr-OMe **11** in quantitative yield. ^{F}Teoc-Val-Thr-OMe **11** was cyclized using PEG-Burgess reagent[12] in 1,4-dioxane and THF (1:1 v/v). After the same work-up procedures, *N*-^{F}Teoc-oxazoline methyl ester **12** was obtained in 70% yield. The oxazoline **12** was dehydrogenated with DBU and bromotrichloromethane in dichloromethane.[13] The crude product obtained by the work-up was purified by silica gel column chromatography to afford *N*-^{F}Teoc-oxazole amino acid methyl ester (^{F}Teoc-Val-MeOxz-OMe; **13**) in 79% yield. Enantiomeric purity of the product was determined to be higher than 95% ee by HPLC with the chiral column. ^{F}Teoc-Val-MeOxz-OMe **13** was deprotected with TBAF in THF. The crude product obtained by the work-up was purified by neutral alumina column chromatography to provide oxazole amino acid methyl ester (H-Val-MeOxz-OMe; **14**) in 61% yield.

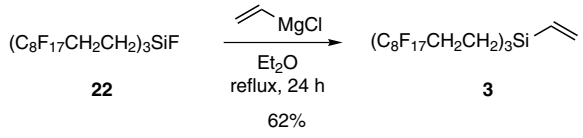
Finally we tried to synthesize bistratamide H from ^{F}Teoc-Val-Thz-OEt **10** and H-Val-MeOxz-OMe **14** (Scheme 4).

At first, ^{F}Teoc-Val-Thz-OEt **10** was treated with TBAF in THF to remove ^{F}Teoc protecting group. After evaporating THF, the residue was extracted with water, chloroform and FC-72. From chloroform layer, deprotected thiazole amino acid ester (H-Val-Thz-OEt; **15**) was obtained in 82% yield. On the other hand, ^{F}Teoc-Val-Thz-OEt **10** was treated with 1 M LiOH aqueous solution in THF and then the reaction mixture was acidified



Scheme 4. Preparation of bistratamide H.

and extracted with FC-72. From the FC-72 layer, *N*-^{F}Teoc-thiazole amino acid (^{F}Teoc-Val-Thz-OH; **16**) was obtained in 98% yield. The two thiazole amino acid derivatives **15** and **16** were coupled by using benzotriazol-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate (PyBOP) and *i*-Pr_2NEt in THF. After the work-up, thiazole amino acid dipeptide ester (^{F}Teoc-Val-Thz-Val-Thz-OEt; **17**) was obtained in 96% yield. ^{F}Teoc-Val-Thz-Val-Thz-OEt **17** was treated with 1 M LiOH aqueous solution in THF. After evaporating THF, the aqueous solution was acidified and extracted with FC-72. From the FC-72 layer thiazole dipeptide amino acid (^{F}Teoc-Val-Thz-Val-Thz-OH;**18**) was obtained in 92% yield. ^{F}Teoc-Val-Thz-Val-Thz-OH **18** was coupled with H-Val-MeOxz-OMe **14** by using PyBOP and *i*-Pr_2NEt in THF. After the work-up, tripeptide methyl ester (^{F}Teoc-Val-Thz-Val-Thz-Val-MeOxz-OMe; **19**) was obtained in 88% yield as amorphous solid. ^{F}Teoc-Val-Thz-Val-Thz-Val-MeOxz-OMe **19** was treated with 1 M LiOH aqueous solution in THF. After evaporating THF, the aqueous solution was acidified and extracted with FC-72. From the FC-72 layer ^{F}Teoc-Val-Thz-Val-Thz-Val-MeOxz-OH **20** was obtained in 90% yield. ^{F}Teoc-Val-Thz-Val-Thz-Val-MeOxz-OH **20** was treated with TBAF to remove ^{F}Teoc protecting group in THF. After evaporating THF, the residue was extracted with FC-72 and methanol. *N*,*O*-Deprotected linear peptide **21** obtained from the methanol layer was dissolved in DMF-CH_2Cl_2 (1:2 v/v) and the solution was added very slowly to a solution of PyBOP and DMAP in DMF-CH_2Cl_2 (1:2 v/v) with maintaining high dilution conditions. The product was purified with a preparative TLC to give bistratamide H in 35% yield. The specific rotation, ^{13}C and ^{1}H NMR spectra and MS analysis demonstrated that the product was the desired compound.[14]



Scheme 5. Attempt to recycle the recovered fluorous silylfluoride.

As to the fluorous product **22** that was obtained from FC-72 layer on deprotection of ^{F}Teoc group with TBAF, we were very pleased to find that a reaction of the fluorous product **22** with vinyl magnesium chloride in FC-72 provided vinyl silane **3** in moderate yield (Scheme 5).[15] ^{1}H NMR spectra of the vinyl silane product **3** was the same as that of the sample obtained by the reaction of tris(perfluorodecyl)silylbromide **2** with vinyl magnesium chloride.[16] Therefore the fluorous product **22** must be tris(perfluorodecyl)silylfluoride and have high purity judging from its ^{1}H NMR spectra in FC-72 (C_6D_6 was used as an external lock and standard).[17] Identification of the fluorous product **22** and optimization of the recycling process are now underway.

In conclusion, we synthesized bistratamide H expeditiously by using the new fluorous protecting group. The isolation of the fluorous intermediates by fluorous liquid extraction was very easy and quick, although the fluorine atom content was just about 48% at the final stage. Optimization of the reactions was carried out as usual by monitoring the reactions with TLC. The enantiomeric purities of the fluorous intermediates were checked by HPLC with a chiral column to find optimal reaction conditions for avoiding racemization of the products. In addition, the fluorous fragment from the fluorous protecting group was demonstrated to be recycled.

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14. Data of synthetic bistratamide H: $[\alpha]_D^{14}$ −103.1 (*c* 0.385, MeOH) (*lit.*$[\alpha]_D^{25}$ −92.9 (*c* 1.1, MeOH)[1a]); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.89–0.99 (m, 12H), 2.14–2.28 (m, 3H), 2.59 (s, 3H), 5.07 (dd, 1H, $J = 5.2$ and 8.5 Hz), 5.36 (dd, 1H, $J = 5.5$ and 8.5 Hz), 5.45 (dd, 1H, $J = 6.6$ and 9.7 Hz), 8.33 (s, 1H), 8.35 (s, 1H), 8.37 (d, 1H, $J = 9.7$ Hz), 8.50 (d, 1H, $J = 8.5$ Hz), 8.54 (d, 1H, 8.5 Hz); ^{13}C NMR (63 MHz, DMSO-d_6) δ 11.5, 18.2, 18.3, 18.4, 18.8, 19.2, 33.0, 34.6, 34.8, 52.6, 54.8, 55.0, 125.0, 125.5, 128.0, 148.0, 148.5, 153.6, 159.2, 159.7, 159.9, 160.7, 168.7, 169.2; MALDI-TOFMS calcd for $C_{25}H_{32}N_6O_4S_2$: 567.1810 $[M+Na]^+$ found: 567.1955.
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16. ^{1}H NMR data of vinylsilane **3**: (250 MHz, FC-72, external C_6D_6 lock) δ 6.39 (dd, 1H, J =3.9 and 14.7 Hz), 6.32 (dd, 1H, $J = 14.7$ and 20.2 Hz), 6.02 (dd, 1H, $J = 3.9$ and 20.2 Hz), 2.39–2.19 (m, 6H), 1.21–1.14 (m, 6H).
17. Data of fluorosilane **22**: ^{1}H NMR (250 MHz, FC-72, external C_6D_6 lock) δ 2.46–2.26 (m, 6H), 1.26–1.19 (m, 6H); CI-MS (negative, *m*/*z*, %) 1387.9 (15), 979.1 (100), 921.1 (91), 551.1 (17), 350.1 (15).