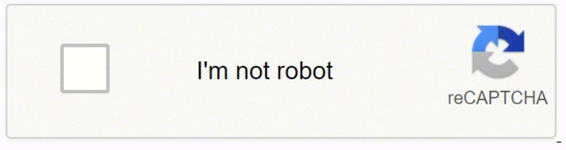
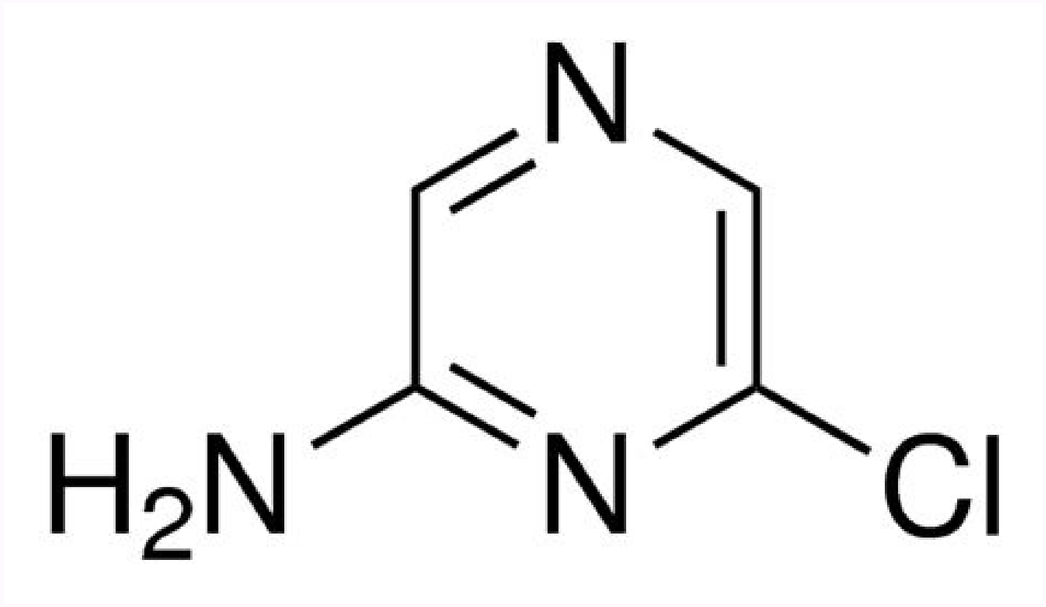
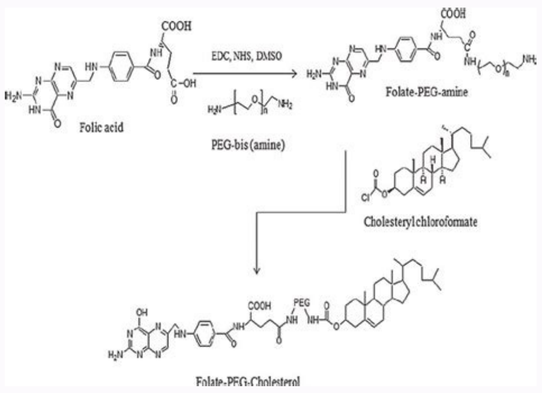
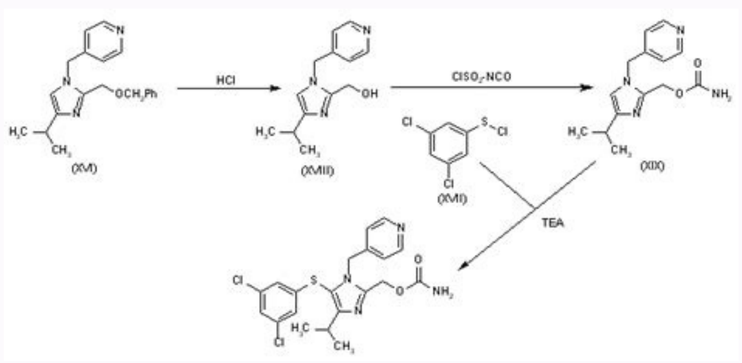


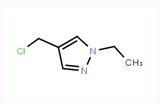
Next

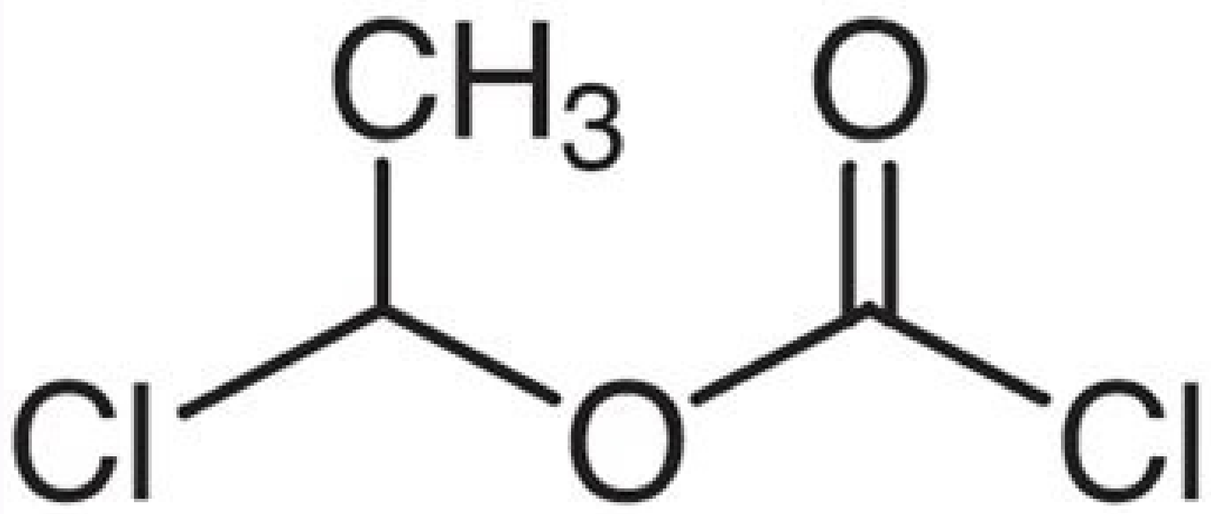
1- chloroethyl chloroformate mechanism











Debenzylation using 1-chloroethyl chloroformate mechanism. 1-chloroethyl chloroformate mechanism.

Astratto N-Benzyl tertiary amines on the reaction with ethyl chloroform give the corresponding debenzylated N-carbamates that on the treatment with I3B:N(C2H5)2Ph complex produce secondary amines. Volume 47, Section 3 p. 569-581 First publication: 29April 2010 Anatabine is a major alkaloid in Nicotiana tabacum and its isomer, isoanatabine, has recently been found in a marine worm. The reduction of 1-methylpyridium iodide with sodium boroidide gave 1-methyl-3-piperidine, which was converted with hydrogen peroxide into N-oxide. The reaction of N-oxide subsequently with trifluoroacetic anhydride and potassium cyanide gave 2-cyano-1-methyl-3-piperidine. His reaction to 3pyridilmagnesis chloride gave (A)-N-methyl-isoanatabine. This has been transformed with m-chlorobenzoic acid into N-oxide which has been N-demethysed with iron (II) sulphate, giving (A)-isoanatabine. The subsequent applications of the literature procedures for N-demethylation for N-oxide decomposition have contributed to the knowledge of the mechanism of this oxidative rearrangement. On the other hand, the reduction of 1-methylpyridium iodide with sodium boroidide and potassium cyanide present from the beginning of the reaction in a two-layer ether system gave 2-cyano-1-methyl-4-piperidine. This has been transformed into (A)-anatabine by the same sequence of reactions used for the synthesis of (A)-isoanatabine. J. Heterocyclic Chem., (2010) The full text of this article hosted in iucr. org is not available due to technical difficulties. Tuberculosis affects about two billion people around the world and causes 1,3 million deaths every year. Chemotherapy solutions are based on drugs developed many years ago, with only one new therapist approved in the last 40 years. the increase of drug resistant strains, there is an urgent need for the development of a Robust drug development pipeline. GlaxoSmithkline has recently placed the structures and activities of 177 anti-tuberculous Leaders novel in the public domain, as well as the results of a continuous optimization of some of the series. Since many of the compounds are born from screening campaigns, their origin was unclear and synthetic pathways in many cases have not been reported. Here we present the efficient synthesis of several analogues of a family of compounds GSK Â ¢ Â Â Â ¢ Â Â Â Â Â Â Â ~~ Ã ¢ Â Â Â using a oxa- Pictet226; â € Ã " Â"; Spengler reaction. The new compounds are attractive from the point of view of the medical chemistry and some were powerful against the virulent strain, suggesting that this class is worthy of further study. The search was carried out using the open source methodology, providing community full access to all raw experimental data in real time. M. Tuberculosis infection resulting in symptomatic tuberculosis (TBC) can be fatal without treatment. In 2012, TBC was responsible for the death of one million people and another million people were infected [1]. Globally, two billion people have latent tuberculosis and are susceptible to develop active tuberculosis. The current first-line treatments include the Ã ¢ â € â € short-course-chemotherapy Ã ¢ † Â Regime, which includes combinations of rifampicin, Isoniazid, pyrazinamide and ethambutol, took for at least six months [2]. These drugs were used since the 1960s; The recent FDA approval of Bedaquilina [3] makes this drug the first new TBT treatment to be approved in forty years. The dissemination of strains partially and totally resistant to drugs makes the development of new treatments priority (preferably targeted by new cellular mechanisms). GlaxoSmithkline (GSK) has recently the anti-TB structures and activities of the small molecules 177 as part of an open data deposit [4]. These leads have been identified outside a pool of 20000 to 20000 chosen by the collection of GSK corporate compounds based on favorable parameters cellular permeability and similar to drugs. Of the 177 cables, seven compounds contained a nucleus of thiophene spurs; these were called Spiros by GSK, represented by GSK2200150A (Figure 1). The members of the Spiros series are excellent starting points for the development of new anti-TB agents. The compounds have been identified following a number of screens that have evaluated their inhibition of the growth of mycobacteria, cytotoxicity and physical properties. The Spiros seem to influence an essential membrane transport protein (MmpL3) of M. tuberculosis [5]. There are no currently approved drugs that target MmpL3, but four structurally dissimilar compounds (C, Figure 1) have been identified as acting on MmpL3 [6]–[9] and a more recent set of indoleamides [10]. In 2012 SQ109 completed a phase IIa clinical trial for pulmonary TB [11]. Spiros analogues are not too similar in structure to these compounds; A further investigation is clearly required on the specific way of action at MmpL3, but it is a desirable property of any new antitubercular compound that should have a different objective than the existing therapeutic one. Screening campaigns frequently use commercial libraries that, understandably, lack synthetic origin. The synthesis of the secondary amine nucleus of the spirocy was incompletely reported in the patent literature and a synthesis of the successful compound GSK (GSK2200150A) was described in academic literature but with incomplete data and limited information on analogue synthesis. [4]–[5], [12]. We have rationalized that the Spiros analogues could be quickly produced from the first core construction using an oxa-Pictet-Spengler reaction followedfinal diversification of the phase from secondary amine 3 (Figure 2). This would allow the rapid synthesis of new Spiros analogues in three stages and and progression of this series in a hit-to-lead campaign. Potential for rapid synthesis of analogue Spiros through a common 2nd intermediate amine 3. (A) an existing bone-painting; Spengler reaction can be used to form the spirocycle nucleus (blue) such as the 2nd amino 3 [12]. (B) Strategy to diversify from 2nd core 3 to produce similar Spiros (C) with variation to piperidine nitrogen (red). Here we describe this work that was carried out with an electronic lab notebook on the Internet [13] and an open source research philosophy that had shown efficiency gains in discovering a synthetic pathway for a drug used in the treatment of schistosomiasis [14]. The license that governs such works is that research can be used for any purpose, even for financial purposes, provided that the project is mentioned. The laboratory notebook, containing a snapshot of the experiments and all data for the period April August 2013, was deposited online [15]. Data on the remaining experiments (late Augusti226;late December 2013) are included in the spreadsheed S1 sheet rather than in the electronic laboratory notebook due to a local technical difficulty at the time of data collection. Our first synthetic approach was the use of compound 5 to make 3 with an oxa-Pictet Spengler reaction (Figure 3). We have adapted the patent procedure (A, Figure 2) [12] using 4-piperidone 5 instead of the corresponding ketal 2, since replacing the ketal with the ketone in the bone-Picture-Bone Spengler reaction should have a limited effect on the reaction result [16]. The ketone is available on the market but has been easily prepared by 4-benzylpiperidone 4 (A, Figure 3) [17] a compound that has been used subsequently. the harsh conditions of cyclicization (excess of triple acid) led to the formation of unobservable mixtures. Core synthesis 70 has been attempted to useAdapted from literature [12]. (A) N - Debenzylation of 4 has been reached under the conditions of hydrogenation of the transfer catalyzed by Palladium [17]. (B) the reaction of ketone 5 with thiopeneethanol 1 in the presence of strong brÃƒÂ¸nsted acids has not produced the expected branches 3. The required reaction variables have been explored to promote cycling, such as the reduction of the quantity of acid, using metanesulfonic less acid acid [18] Ã ¢ â,¬ "[19], introducing a non-polar solvent (toluene or dioxane) and warming up the reaction. These efforts have led to a partial recovery of the tiofen starting material Together with a complex mixture of products or decomposition and the formation of polar compounds that have not been identified. The Ketal 2 can therefore be crucial in this transformation in which a setup of reactivity and precise conditions are required to promote conversion but Not the decomposition. However, the formation of this Ketal would unfavorably introduce another step into the synthesis (A, red, figure 4). We therefore created a stringent Alternatively to access secondary amine 3: carry out the spengler reaction of OXA-Picturet using 4 before removing the N-Benzil group (B). (A) the route attempted according to the patent literature procedure [12]. The dashed lines represent the additional step (red) required to try the cycling strictly under the patent conditions. (B) The magazine strategy: cycling to give 6 followed by the debenance to give the 2nd Amine 3 (blue). The first step of the magazine strategy has proved to be effective; The N-Benzilated nucleus (6) was obtained in a good constant yield on a series of repetitions (A, figure 5). There was promoted by 1.5 equivalents of metanesulphonic acid instead of triple acid, the first is easier to manage. to counteract the reduced acidity, the reaction temperature has been increased. lowering thethe load or reaction time gave a mixture of the product 6 and the raw material; ketone 4 was inseparable from product 6 in the post-reaction process or by flash chromatography. The metansolphonic reaction mediated by the acid initially carried out was the most effective to obtain cleanly the desired spirocyc 6. Execution of the revised strategy towards the synthesis of the core of spirocycle as 2nd Amine 3.A) Acid-mediated cyclicization. B) Try to synthesize the 2nd amine by catalytic hydrogenlysis. (C) 1-chloroformyl chloroform is effective in producing secondary amine 3. (D) 2-chloroethyl chloroform led to an incomplete deprotection of 6. The next step was the removal of the N-benzile group from 6 to give the secondary amine 3 (from B to D, figure 5). Spirocycling 6 N-benzilate was stable in a variety of palladium-catalyzed hydrogenlysis conditions (B). The transfer hydrogenation conditions used in the preparation of 4-piperidinone 5 were ineffective; starting material 6 was recovered. Successive attempts were made using different pressure combinations (hydrogen gas up to 8.3 bar), transfer hydrogenation and extended reaction times. In all attempts, the starting material was recovered with minimal material loss. Instead we turned to conditions of debenzilation mediated by 1-chloroetyl chloroformate 7 (green), which gave the wait secondary amine 3 (blue) in excellent yield (C, Figure 5). Debenzilation proceeds presumably by means of a carbamate intermediate following the reaction of the raw material 6 with chloroform 7 and the loss of benzile chloride [20]â–[21]. The subsequent decarbossilation, promoted by excess methanol and reflux conditions, produceddesired secondary 3 [20]â[21]. The isolation of carbamate 9 with the use of 2-chloroethyl chloroform 8 is consistent with the proposed mechanism (D); initial The pace would not be affected given the similar reactivity of the functional groups of chloroform, but the methanol attack on secondary carbon to lose Ĩ²-chloride would be less likely that the tertiary carbon attack to lose the ±-cloride. The secondary 3 amine 3 was obtained, ready for diversification of the final phase in the rendering of ¼84% on two passages. Nursing from secondary amine 3 Using the conditions of reducing amuminates and the acilation conditions enabled for the rapid synthesis of a variety of compounds in a moderate yield to a good yield (figure 6). Sodium triacetoxybohydride sodium reducing amimination procedure has been adapted from literature [22] Ã ¢ â,¬ "[23]. The Acilation of Line 3 has been reached using Aroyl chlorides. All candidate compounds are Stati designed to show acceptable calculated logp values. Acilation products from 16 to 18 and ARYLPyrrole 14 showed twisted NMR spectra twisted. The 13C {1H} -NNR spectra from 16 to 18 contained the signals expected from carbon atoms In the carbon groups (from 165 to 175 ppm in CDCL3) which indicate the formation of Bond Bond, but 1h - 13c {1h} Heteronuclear single quantum correlation spectroscopy (HSQC) was required to clarify the Piperidine region 13c { 1h} (A, figure 7); the wide 1h-related signals related to the Alifatic region of the spectrum of 13c {1h} (b) were consistent with piperidine-ring protons and all environments have been accounted for. The large signals observed for the Methylene protons on the Anony LLO containing oxygen in compounds containing a bond of amide exocyclica (ie compounds 16 "18) most likely deriving from the chirality exposed by individual rothants (C and D), which, therred in dynamic balance through an Achiral intermediate (B) make Protons to these diastereotopic carberians. Further experiments were carried out on the product acylated 16, which showed consistent temperature and magnetic (E) field dependence rapid rotation of the amide bond; at higher fields or peaks of lower temperatures for individual rotators, and their more convoluted split patterns, have become clear. The piperidine nitrogen signals of the hardened products may be displayed by HSQC experiments. The 1H-NMR and 13C{1H}-NMR spectra shown on the X- and on the y axes of the HSQC spectra respectively are projections of the corresponding monodimensional NMR experiments and are displayed for clarity. (A) the aliphatic region of spectrum 1H-13C{1H} HSQC of 16; The red arrows indicate the 1H signals corresponding to the piperidine protons (connected to the red ring of the structure). The corresponding piperidine carbon signals on axis y (circular red) are not clear in spectrum 13C{1H}. (B) The rotation around the amide bond generates chiral rotators (C and D) dictated by the benzamide system, which makes the methylene protons in the oxygen ring diastereotopic, (E) Variable magnetic field temperature and NMR experiments showing the carbonescence of methylene signals for the compound 16. At lower temperature, ring protons containing diastereotopic oxygen (E) showed a higher coupling than the order, resulting from individual rotators (Figure S39) and the 13C{1H} NMR showed the complete resolution of the carbon piperidine ring signals (Figure S40). Raw data can be found in Dataset S1. Activities of compounds containing the nucleus of the spirocycle (3, 6, 9a-18) were determined against the virulent M.tuberculosis (H37Rv) (Table 1). Initially, M. tuberculosis H37Rv was exposed to a single dose of 100-AM compound for seven

days, and survival was determined in comparison to bacterial cells treated with a microtitre analysis Resazurin of growth inhibition the potency of compounds showing activity at 100 µM was determined by calculating the concentration of the drug by inhibiting 50% of thegrowth (IC50). Ã excellent activity was observed Inhibition against H37Rv for compounds containing N-benzyl\/pyrrole (6, 10, 11, 13 and 14) centers other than for 12; spirocyclic 1 containing cyclohexyl, secondary amine 3 and N-acyl spirocycles (9, 16-18) were inactive. The presence of the N-CH2-Ar group seemed to be a necessary but not sufficient condition for a business significant against H37Rv, but the functionality It was damaging to the potency of the molecules. The new compounds 13 and 14 were the most powerful¹ with activities comparable to the anti-TB compounds of Spiros identified and developed by GSK [4]â[5]. Activity anti-tuberculosis of the synthesized Spiros analogs. EntryCompoundCLogPH37Rv IC50 (Î1.M)THP IC5 (Î1.M)1 3 0.83>100n\/a2 6 3.152003 9 2.1>100n\/a4 10 3.01.251005 11 3.010>2006 12 2.2>100n\/a7 13 3.81.25 508 14 5.4* 1,256.39 15 3.2>100n\/a10 16 1.7>100n\/a11 17 2.6>100n\/a12 18 2.6>.100n\/aThe toxicity of compounds showing activities anti-H37Rv Ã¨ was evaluated using the human monocytic cell line THP1 (Table 1). The IC50 against THP Ã¨ was calculated and Ã¨ was compared with the IC50 calculated against M. tuberculosis H37Rv. Compounds 6, 10, 11 and 13 showed toxicity THP1 at relatively high concentrations (>50 Î1/M), suggesting the potential for future development of these compounds. Compounds 6 and 11 were less toxic than the original GSK structure (10) but were also less powerful against H37Rv. Compound 14 was highly active against H37Rv, however it was toxic against THP1 in the range of low Î1.M. A three-step summary of new tuberculosis drugs that will provide quick access to powerful compounds that could be used in a future evaluation of this series. CiÂ² should help both in the synthesis of existing analogs for the examination of their pharmacokinetics both in the synthesis of several new analogs in this series to optimize the potency and the drug. drug.and © to a further mechanism of action studies. Future participants in these efforts are encouraged to adopt the open platform that has already been developed for the sharing and collaboration of complete data. The general synthetic and analytical methods are detailed in text S1. RM Raw data for all compounds are available at the eScholarship repository of Sydney University [25.] The open electronic laboratory book for April-August 2013 experiments is available at The University of Sydney eScholarship Repository [15;] all other experiments are summarised in Spreadsheet S1. This compound exists in literature, but no data is reported [22.] To a mixed solution of 6 (2,3 g, 7,7 mmol, 1 equiv.) in THF anhydrous (200 mL) under argon to 78o C A chloroethylic chloroformed (1.6 mL, 15 mmol, 2 equiv.) The reaction mixture was mixed for 30 minutes then allowed to warm up at rt. THF was removed under reduced pressure leaving a volume residue of 10-mL which has been diluted with methanol (200 mL) and reheated for 20 min. The clear brown solution has now been concentrated under reduced pressure to give the raw product as brown foam (2,8 g). 5.5.5.5.5., H.2.5., H.3.5. HMBC (Figure S4) spectra also supplied; Anal! Calcium. C, 63.12; H, 7.22; N, 6.69. Found: C, 63.46; H, 7.56; N, 6.61.a A vigorously agitated solution of thiopeneethanol (0.50 ml, 4.5 mmol, 1 equivoting) and 1-benzyl-4-piperidinone (0.80 ml, 4.5 mmol, 1 equivoting) in toluene (50 ml) Metanesulfronic acid (0.29 ml, 4.5 mmol, 1 is added) has been added. The reaction mixture has been heated to reflux (oil bath at 130 Â ° C) for 16 hours and allowed to cool to RT. The mixture has been diluted with ethyl acetate (50 ml) and washed with saturated Nahco3 (30 ml). The aqueous fraction has been extracted with ethyl acetate (2-30 ml), further basifix with solid sodium hydroxide (4.0 g) and extracted with ethyl acetate (2-30 ml). The combined organic fractions have been dried (NA2SO4) and concentrated under reduced pressure to give the raw product as a dark brown oil (1.7 g). The raw material has been purified by the flash chromatography on the silica (10 "50% of ethyl acetate / eSASI) to give the title compound as a pale yellow oil (1.2 g, 86%); ÃžÃ½max (film) / cmÂ ¢ '1 2936, 2813, 1075, 854, 672; Ãž'h (500 mhz; cdcl3) 7.37 - 7.31 (m, 4 hours), 7.27 - 7.24 (m, 1 h), 7.06 (D , J â¡ = Ã ¢ â,¬ © Å¡5.2 Hz, 1 h), 6.82 (D, J Å¡ = Ã ¢ â,¬ © Å¡5.2 Hz, 1 h), 3.93 (Tapp, J Ã © = Ã ¢ â,¬ Ã © Å¡5.4 Hz, 2 h), 3.56 (s, 2 h), 2.82 (Tapp, JÃ ¢ Ã ¢ â,¬ Å = Å¡5.4 Hz , 2 h), 2.74 - 2.71 (M, 2 hours), 2.43 - 2.38 (m, 2 hours), 2.01 - 1.95 (M, 2 hours), 1.86 Ã ¢ â,¬ " 1.82 (m, 2 h) (figure S5); Ãž'c (126 MHz; CDCL3) 141.3, 138.6, 132.7, 129.4, 128.3, 127.1, 124.5, 122.3, 73.3, 63.5, 59.1, 49.2, 36.2, 26.0 (figure S6); 1h Ã ¢ â,¬ "13C HSQC (Figure S7) and 1h Ã ¢ â,¬" 13C {1h} HMBC (Figure S8) Spectra also supplied; HRMS (ESI) 300.14161 ([M + H] +), Calct. For C18H22NOS + 300.14166.This procedure has been adapted from literature [20] [22]. Compounds 10 Ã ¢ â,¬ "15 were prepared using this method. To a stirred secondary amine solution 3 (1 equivalent) and or the appropriate ketone (1.1 Equiv) to dichloromethane anhydrate (at 50 mm of 70) was added sodium triacetossyborusride (1.5 Equiv.). The It was mixed with rt under argon for 18th and then turned off by pouring over the saturated NaHCO3 solution. The aqueous phase was extracted with dichloromethane (twice). The combined organic fractions have been dried (Na2SO4) and concentrated under reduced pressure. The raw product has been purified by flash chromatography on silica to provide the corresponding tertiary product of amine. Compounds 16A have been prepared using this method. A mixed solution of secondary amine 3 (1 equivalents) and triethylamine (2 equivalents) in dichloromethane anhydrous (from 0.2 M of 70) under argon has been cooled in an ice bath in brine. Appropriate acid chloride (1 equivalents)benzoyl chloride, 2-bromobenzoyl chloride or 4-bromobenzoyl chloride has been added slowly. The mixture has been mixed at temperature for the 15 min, slowly allowed to warm up and mix for another for the 12th to 15h. The reaction has been switched off by pouring over the saturated NaHCO3 solution. The aqueous phase was extracted with dichloromethane (three times). The combined organic fractions have been dried (Na2SO4) and concentrated under reduced pressure. The raw product has been purified by flash chromatography on silica to give the corresponding amide product. This procedure has been adapted by literature [22]. A mixed solution of 3 (0.40 g, 1.4 mmol, 1 equivalent.) in THF anhydrous (35mL) under argon other than argon; 2-chloroethyl chloroform (0.18 mL, 1.mm7 ol, 1.3 equivalents) has been added. The reaction mixture was mixed at 176C 78th to 30min h to allow heating. The solvent has been removed under reduced pressure and the residue of brownish has been suspended in methanol (40mL) and heated at the outlet for 1 h. The clear brown solution has now been concentrated Reduced pressure to give the raw product as yellow oil (22666;;0.5 g) The raw material has been purified by flash chromatography on silica (10% ethyl acetate/CH2Cl2) to give the compound title as colourless oil that when taken to 4.A.C (0.35 g, 82%); mp 57A 60-C; Maximum (film) /CMA 1 2953, 2923, 1072, 1050, 741, 654; I'm going to do it (500 MMHz; CDCDCDC3 7,08 (d, JA =5,2 Hz, 1H), 6,72 2 (d, JAA=5,2 HHH, 4,36 (tapptapptapptapptapptapping, 5,2 2 HHHHHHH, 4,4 4 4 (br, 2H), 3,94 (tapp tapp tapp, jA=5,4 HHHHz, 2 H H H), 3,771 1 1 1 (t, when you see see a A A A=5.6 H 6 Hz, H, H H, H, H H H H H H H, 3,21212121212, 2, 2, 2, 2,832 2 2,832 2 2 2 2 2 2 2 2,8383(t, jA = 5,4 Hz, 1H), 1.84-1.81 (m, 1 H) (Figure S9); I'C (126 MHz; CDCl3) 154,9, 140,3, 132,9, 124,1, 122,7, 73,2, 65,0, 59,4, 42,5, 39,9, 25,9 (Figure S10); HRMS (ESI) 280,10 thousand ten ([MA CI] +) path. for C14H18NO3S + 280,10019 thousand; 1H-13C HSQC (Figure S11) and 1H-13C {1H} HMBC (Figure S12) spectra also provided; HRMS (ESI) 338,05867 mile ([M + Na] +), all. for C14H18ClNO3SNa + 338,05881 thousand; Anal. Cale! for C14H18ClNO3S: C, 53,24; H, 5,74; N, 4.44. Found: C, 53,21; H, 5,77; N, 4,40. 13C {1H} NMR signals are missing or obscured due to the whole carbamate rotator. Prepared according to general procedure 1. After purification by flash chromatography (1A,100a,0.1,CH3OHHl3E,NH4OH), the compound title was obtained as a colourless oil that solidifies a colourless solid when taken -20mg,58%; 106A 109A C; Maximum (film) /CMA 1 2926, 2813, 1505, 1068, 886, 648; H (500 MMHz; CDCCC3) 7.06 (d, JA =5.1 Hz, H), 6,88 (Sapp, H), 6.846 6,79 (m, 3H), 4,25 (S, 4 H), 3,92 (tap, ja, in a =5,3 3 Hz, 2H), 3,45 (s, 2H), 2,82 (tap, jA=5,3,3,3 HHHz, Hz, H, 2,71 2,71 (by by by by by by by by by by by by by by by by by by by by by the way, by by by by by by by by by by by by by 11.2.2.2.2.2.2.2.2.2.2 Hz 2H), 2,37 (tapp, jA = 11.9 Hz, 2H), 1,97 (tdapp, jA = 13,2, 4,0 Hz, 2 H, 1,84 (d, jA = 13,0 Hz, 2 H) (Figure S13); I'C (126 MHz; CDCl3) 143,4, 142,7, 141,4, 132,7, 132,0, 124,6, 122.40, 122.30, 118.1, 117.0, 73.4, 64.51, 64.49, 62.9, 59.1, 49.1, 36.3, 26.0 (fig S14); 1H-13C HSQC (Figure S15) and 1H-13C {1H} HMBC (Figure S16) spectra also provided; HRMS (ESI) 358,14712 mile ([M + H] +), all. for C20H24NO3S + 358,14714 thousand; Anal. Cale! per c, c, c, c, c, c, c, c.H, 6.49; N, 3.92. Found: C, 66.55; H, 6.54; N, 3.88. Discrepancy in the CHN analysis noted, but consistent data with 4m + H2O, I.e. Calcd. for c80H94N4O13S4 66.36; H, 6.54; N, 3.87.prepared according to general procedure 1. After purification by flash chromatography (2-1000.2, ch3ohâ¶ch2cl2â¶nh4oh), the compound of the title was obtained as an incolored oil that solidified to a colourless solid when brought to 4 ° C (37 mg, 44%); max © max max max max max max max max max max max max max max max max max max max max max max max max max max max max max max max max max max max max max max max max max max , max Î'c (126 MHz; CDCl3) 147,7, 146,7, 141.3, 132.73, 132.56, 124.5, 122.48, 122.33, 109.8, 108.0, 101.0, 73.4, 63.3, 59,1, 49,1, 36.3, 26.0 (Figure S18); HRMS (ESI) 344.13146 ([M + H] Calcium for c19h21No3s: C, 66,45; H, 6.16; N, 4.08. C, 66.59; H, 6.26; N, 3.98.prepared under general procedure 1. Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo , Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Dopo Î'c (126)CDCL3) 146,7, 144,9, 141.1, 132.6, 129,9, 124.4, 122.38, 122.19, 114.2, 112.0, 73.3, 59.0, 55.8, 49.0, 49.0,35.9, 27.0, 25.9, 25.0 (figure S20); 1H – 13C HSQC (figure S21) spectrum also provided; HRMS (ESI) 346.14711 ([M+H]+), kicked. for C19H24NO3S+ 346.14714; Anal. Calculated. for C19H23NO3S: C, 66.06; H, 6.71; N, 4.05. Found: C, 65.88; H, 6.91; N, 3.87. Prepared according to general procedure 1. After purification by flash chromatography (3â¶âÂ¶âÂ¶â 0.3, CH3OHâÂ¶ mp 106â - 109Â C; Î1/2max (film)/cmâ€TMÂ 1 2923, 2816, 1489, 1076, 1016, 854, 646; (500 MHz; CDCl3) 7.29 (sapp, 4 H), 7.07 (d, J, 126; 128; Composition;;; ;;;;;;;;;2 Hz, 2 Hz, 2 H), 2.52 (s, 2 H), 2.82 (tapp, J226; 126; 3.5252 (s, 2 H), 2.822.82(e.g. 2), 2 2 Hz, 2 H), 2 2 2 2 2 2 2 H 2, 2), 2,52525252525252525252525252525252525252525252525252525252525252522(2(2)2 (2), 2, 2, 2, 2, 2, 2(2, 2(2, 2(2), 2(2, H2, 2(2, H), 2(2, H), 2(2, H), 2(2, H), 2(2, 2(2, H), 2(2, H), 2(2, 2(2, H), 2(2, H), 2(2, 2(2, H), 2(2, H), 2(2, 2(2, 2(2, H), 2(2, 2(2, H), 2), 2(2, 2(2, 2(2, 2(2, 2(2, 2(2, H), 2), 2, 2(2, 2(2, 2, 2), 2), 2, 2, 2), 2 126 MHz; CDCl3) 141.2, 137.3, 132.8, 130.6, 128.5, 124.5, 122.4, 59.1, 49.2, 36.3, 26.0 (figure S23); HRMS (ESI) 334.10268 ([M+H]+), calcined. for C18H21C1NOS+ 334.10269; Anal. C18H20ClNOS: C, 64.75; H, 6.04; N, 4.20. Found: C, 64.56; H, 6.08; N, 4.16. Prepared according to general procedure 1. 3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3. C (126)CDCl3) 163.0, 161.0, 140.6, 135.0, 135.0, 132.7, 130.130-F (471 MHz; CDCl3) -113.8; HRMS (ESI) 411.19012 ([MOTHER Cl]+), calcinate. for C2H28FN2OS 411.19009; Anal. Anal. for C24H28ClFN2OS: C, 64.49; H, 6.31; N, 6.27. Found: C, 64.05; H, 6.14; N, 5.95.Prepared according to general procedure 1. 2,316,315,315,315,316,316,315,315,316,315,315,315,315,315,316,315,315,315,315,315,315,315,315,315,315,315,315,115 for C85H127N5O6S5: C, 69.20; H, 8.68; N, 4.75.Prepared according to general procedure 2. 116, H1, H1, H1, H1, H1, H1, H1, H1, H1, H1, H1, H1, H1, H1, H1, H1, H1, H1, H1, for336.10287; Anal! Calcium. for C18H19NO2S: C, 68.98; H, 6.11; N, 4.47. Found: C, 68.03; H, 6.05; N, 4.44. The discrepancy in the CHN analysis was observed, but the data consistent with 4M + H2O is the calculation. for C72H78N4O9S4: C, 68.00; H, 6.18; N, 4.41. 13C{1H} signals are missing or obscured due to rotators around the starch bond. The signals were displayed using the spectrum 1H to 13C HSQC (Figure S30) and completely resolved to 270 K (Figure S40). NMR variable temperature data for this compound can be found in Dataset S1. Prepared according to general procedure 2. 5.5.5.5. (See also: H. 185.) Found: C, 55.88; H, 4.89; N, 3.45. 13C{1H} signals are missing or obscured due to rotators around the starch binding. The discrepancy in the CHN analysis was noted; the data correspondence sample containing

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