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Synthesis of new diverse macrocycles from diol precursors

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ABSTRACT

The formation of a library of diverse macrocycles with different ring sizes from two easily accessible building blocks is presented. Reacting diol precursors with electrophilic reagents lead to 17-membered sulfites and 19-membered malonates in 34–79% yield. Double-reductive amination of dialdehyde analogs of the diol precursors leads to 15-membered amines in yields ranging from 9 to 60%, reflecting large differences in reactivity based on steric environment.

1. Introduction

Macrocyclic compounds are attractive targets within drug discovery due to the fact that naturally occurring macrocycles often display diverse and interesting biological activities. This arises from several structural advantages characteristic for this compound class. Macrocycles are conformationally preorganized, enabling them to bind selectively to targets with minimal entropic loss. However, they have a certain flexibility, which, in combination with their functionally independent subregions, enables them to bind non-covalently to each other or to mediate the assembly of other macromolecules by non-covalent interactions. Furthermore, they have the ability of burying away polar functionalities, leading to improved membrane permeability as compared to their linear analogs. Proteolytic and metabolic stability is also improved as a consequence of the reduced accessible conformational space.[1]

The substructures of naturally occurring macrocycles provide valuable inspiration for the design of new synthetic macrocycles, because of the above mentioned biological activity of this compound class. Substructures frequently present in naturally occurring macrocycles are, for example, polyketides, heterocycles, peptide, biphenyl, and (bi)aryl ether domains.[2] A drawback of traditional natural product chemistry is the often complex structures and the synthetic effort thus required. Hence, an approach combining natural product drug discovery, and combinatorial chemistry has been suggested.[3,4] This strategy, designing synthetic compounds from easily accessible building blocks containing naturally occurring substructural motifs, and hence providing rapid access to synthetic libraries, is providing an increased chance of finding a potent drug. Despite the challenge in forming large ring systems, macrocyclic compounds are interesting targets for this strategy and the generation of libraries of macrocycles has received significant attention recently.[5]

Encouraged by our recently reported method on formation of macrocyclic rings from diol precursors,[6] we were interested in generating a library of diverse macrocycles based on this strategy. According to the above, we aimed at producing macrocycles in a few diversity-generating steps starting from two simple building blocks, one containing a heterocycle (triazole) and one containing a hydroxy alkene (a fragment inspired by polyketides). Four structurally isomeric diol precursors are formed through combinations of the two building blocks by esterifications. These are then cyclized, either in one step by reaction with bis-electrophilic reagents, or in two steps by forming the dialdehyde derivatives and then reacting them with a nucleophilic reagent.

2. Results and discussion

The building blocks for the synthesis of diol precursors were readily obtained in good yields from simple, commercially available starting materials (Scheme 1 and 2). Substitution of 4-chlorobutyl benzoate with sodium azide, followed by a copper(I) catalyzed alkyne/azide cycloaddition reaction[7] of the resulting azide with TBDMS protected propargyl alcohol afforded the protected triazole building block **1** (Scheme 1). Reductive cleavage of the benzoyl group gave one of the desired alcohol derivatives **2** (ready for esterification). The other desired alcohol derivative **4** was obtained by

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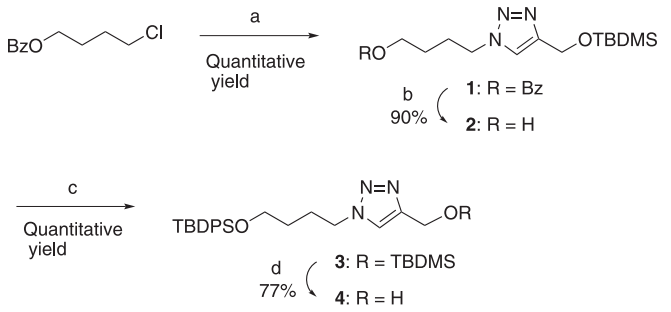
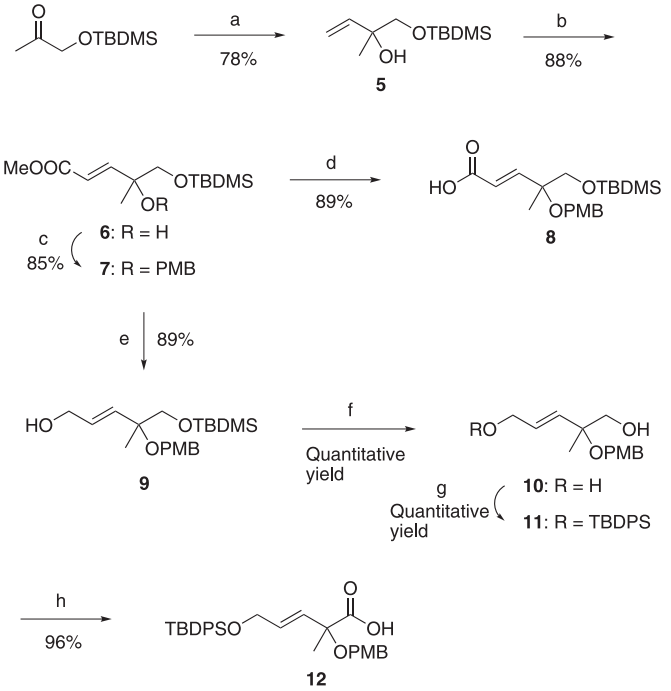
TBDPS protection of **2** and subsequent selective monodeprotection by acidic solvolysis. Preliminary attempts to use a triphenylsilyl (TPS) ether as a protecting group instead of TBDPS did not give the desired selectivity, as the TPS group was found to be more prone to hydrolysis than the TBDMS group.



Scheme 1. Reagents and conditions: (a) (i) NaN_3, *n*-Bu_4NI, DMF, 60 °C, (ii) *tert*-butyldimethyl(prop-2-ynyloxy)silane, DIPEA, CuI, THF; (b) DIBAL-H, CH_2Cl_2, −78 °C; (c) TBDPSCl, imidazole, DMF; (d) PPTS, MeOH, 55 °C.

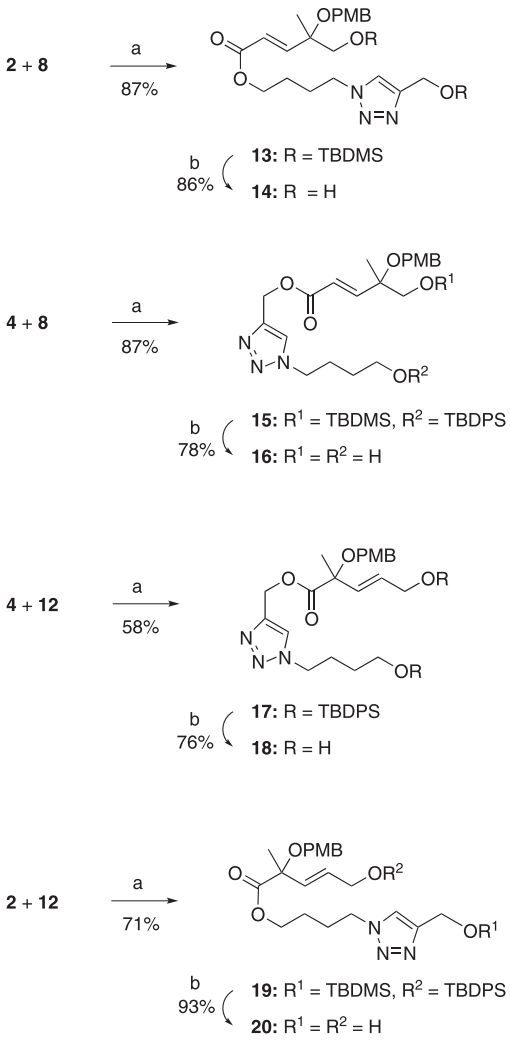
Grignard reaction of TBDMS protected hydroxy acetone with vinyl magnesium chloride (giving 5[8]) followed by a cross-metathesis reaction[9] with methyl acrylate gave the (*E*)-enol building block **6**[10] (Scheme 2). The Hoveyda–Grubbs second generation catalyst[11] was more efficient in this transformation than the Grubbs second generation catalyst.[12] Interestingly, despite the reaction being somewhat slower with 0.5% catalyst loading as compared to 5%, we found the overall conversion to be higher with the lower loading.



Scheme 2. Reagents and conditions: (a) vinyl magnesium chloride, THF, 0 °C; (b) Hoveyda-Grubbs second gen. cat., methyl acrylate, CH_2Cl_2, 40 °C; (c) PMBTCA, $La(OTf)_3$, toluene; (d) LiOH, THF/H_2O 3:1; (e) DIBAL-H, CH_2Cl_2, −78 °C; (f) TBAF, THF; (g) TBDPSCl, imidazole, CH_2Cl_2, −78 °C; (h) (i) DMSO, $(COCl)_2$, −78 °C, Et_3N, (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, THF.

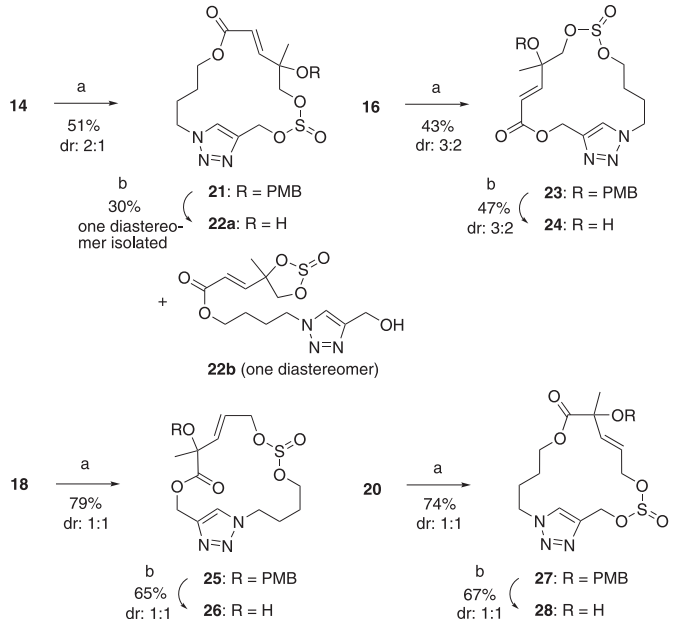
PMB protection of **6** with *p*-methoxybenzyl trichloroacetimidate (PMBTCA)[13] under mild conditions[14] gave **7**, which could be hydrolyzed under basic conditions to yield one of the desired carboxylic acid derivatives **8**. The alcohol **9** was obtained from **7** by reductive cleavage of the methyl ester. Deprotection with TBAF went smoothly, giving the diol **10** in an excellent yield. Most satisfyingly, the allylic hydroxy group could be selectively TBDPS protected at −78 °C in dichloromethane. Swern[15] and sodium chlorite[16] oxidations yielded the other desired carboxylic acid **12**. Preliminary attempts to selectively cleave the TBDMS group from the TPS protected analog of **9** proved unsuccessful for the same reason as specified above for the triazole building block.

The alcohols **2** and **4** were combined with the carboxylic acids **8** and **12** by carbodiimide promoted esterifications[17] (Scheme 3) yielding the four esters **13**, **15**, **17**, and **19**, which were deprotected smoothly with TBAF to give the desired diol precursors.



Scheme 3. Reagents and conditions: (a) EDC·HCl, DMAP, CH_2Cl_2; (b) TBAF, THF.

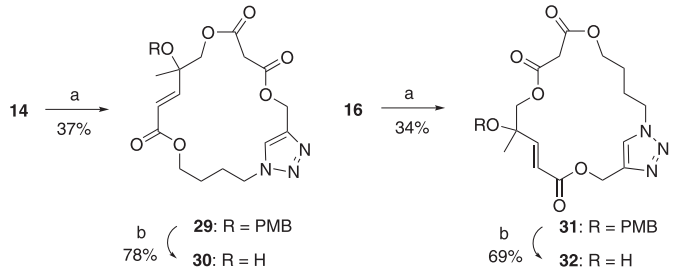
The diols **14**, **16**, **18**, and **20** were treated with thionyl chloride, triethylamine and DMAP under our standard conditions[6] to obtain the 17-membered macrocyclic sulfites **21**, **23**, **25**, and **27**, respectively (Scheme 4). The sulfites were obtained in yields ranging from 43 to 79% reflecting a difference in the steric environment of the cyclization precursors. This is further emphasized by the fact that the diastereomeric ratio of **21**, formed from the most sterically hindered diol precursor, differs from the diastereomeric ratios of the other sulfites in being 2:1 as compared to 1:1 (or 3:2). Not surprisingly, cyclizations of the two least sterically hindered diol precursors **18** and **20** result in higher yields than cyclizations of the more hindered substrates **14** and **16**.



Scheme 4. Reagents and conditions: (a) $SOCl_2$, Et_3N, DMAP, CH_2Cl_2; (b) DDQ, CH_2Cl_2/H_2O 18:1.

Subsequent deprotection of the PMB ethers with DDQ to obtain the sulfites **22a**, **24**, **26**, and **28** resulted in yields ranging from 30 to 67%. The low yield for the deprotection of **21** is caused by lability of the product to column chromatography. This was proven by the isolation of a five-membered cyclic sulfite by-product **22b** formed upon nucleophilic attack by the tertiary hydroxy group on the macrocyclic sulfite. The identification of the product **22a** and the by-product **22b** as single diastereomers confirms that only one of the diastereomers of the deprotected sulfite is susceptible to the intramolecular transesterification of the sulfite.

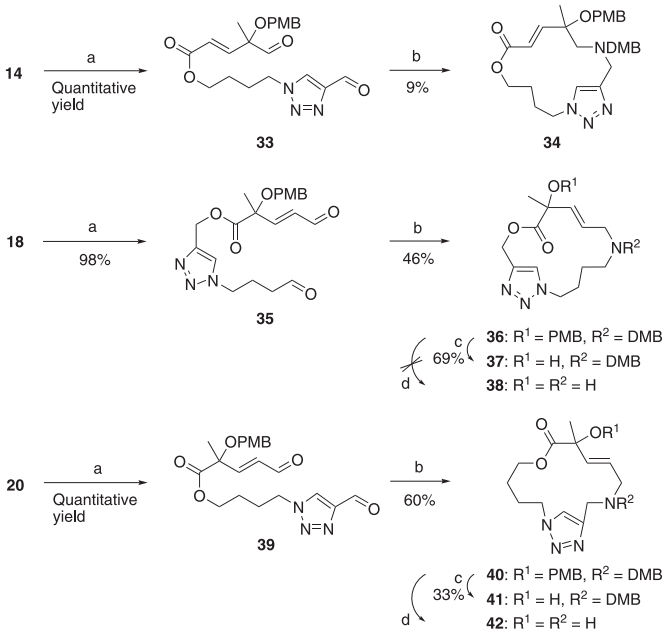
Next, we were interested in extending the above cyclization method to the formation of malonates. Diol precursors **14** and **16** were treated with malonyl chloride under the above conditions, giving the 19-membered malonates **29** and **31** (Scheme 5) in 37 and 34% yield, respectively. Thus, the yields for formation of malonates are slightly lower than for the formation of sulfites, possibly related to the difference in ring sizes formed and/or the relative reactivity of the reagents.



Scheme 5. Reagents and conditions: (a) malonyl chloride, Et_3N, DMAP, CH_2Cl_2; (b) DDQ, CH_2Cl_2/H_2O 18:1.

The malonates were deprotected analogously to the sulfites, giving **30** and **32**. The products were obtained in higher yields than their sulfite analogs, presumably because the malonates are more stable than the sulfites.

Our next target was the 15-membered macrocyclic amine **34** (Scheme 6). The dialdehyde cyclization precursor **33** was prepared by oxidation of **14** in an excellent yield. For this reaction, IBX[18] was found to be superior to the Dess–Martin periodinane[19] as oxidizing agent. Our choice of amine was 3,4-dimethoxybenzylamine ($DMBNH_2$) since it has been reported that removal of the DMB group from a dialkylated amine can be accomplished under mild conditions by the use of DDQ.[20] Unfortunately, double-reductive amination of **33** by use of our previously reported method[6] resulted in only 9% yield of the product **34**. The reason for this low yield was likely to be found in the steric environment of the α,α,α-trisubstituted aldehyde group of **33**. As several attempts to optimize the yield by altering the reaction conditions (reducing or increasing the concentration, change of reductive agents and amines, addition of acid and longer imine formation times) failed, we decided to investigate the cyclizations of the two less sterically hindered dialdehydes **35** and **39**, obtained in excellent yields from **18** and **20**. We were pleased to find that the products **36** and **40** of these cyclizations were obtained in highly improved yields, 46% and 60%, respectively. Thus, these results confirm that **33** is too sterically hindered to undergo double-reductive amination in a satisfactory yield.



Scheme 6. Reagents and conditions: (a) IBX, CH_3CN, 55 °C; (b) $DMBNH_2$, $Na(OAc)_3BH$, CH_2Cl_2; (c) DDQ, CH_2Cl_2/H_2O 5:1; (d) DDQ, CH_2Cl_2/MeOH 9:1.

The deprotection of the amines turned out to be a very slow reaction, especially for the removal of the DMB group. Hence, the PMB group of the amines **36** and **40** could be selectively cleaved by use of 3 equiv of DDQ, yielding the amines **37** and **41**. Several attempts at the full deprotection of **40** to **42** were carried out with DDQ and CAN; use of the former was found to give little conversion whereas use of the latter was unsuccessful. It has been reported that deprotection of DMB protected amines can be inefficient for some substrates.[21] Substituting the usual biphasic CH_2Cl_2/H_2O solvent to a miscible solvent (CH_2Cl_2/MeOH 9:1) led to the highest conversion, although the use of as much as 20 equiv of DDQ over 7 days gave a modest NMR yield of 15%. Attempts at the isolation of **42** (verified by LCMS) from a mixture of the amines **41** and **42** by flash column chromatography were not successful, presumably due to the two compounds having the same R_f value. Unfortunately, the full deprotection of **36**–**38** was not successful by use of the above conditions.

3. Conclusion

We have demonstrated that a library of diverse macrocycles with different ring sizes and functionalities can be formed in a few

steps from simple building blocks containing primary alcohols. The structural and biological properties of the macrocycles are currently under investigation.

4. Experimental section

4.1. General

Starting materials, reagents, and solvents were purchased from Sigma–Aldrich Chemical Co. and used without further purification. Reactions involving air or moisture sensitive reagents were carried out under N_2. CH_2Cl_2, DMF, and DMSO were dried over 4 Å molecular sieves. THF and toluene were distilled from Na under N_2. Et_3N was distilled from CaH_2 under N_2. TLC was performed on Merck aluminum sheets precoated with silica gel 60 F_{254}. Compounds were visualized by charring after dipping in a solution of *p*-anisaldehyde (10 mL of H_2SO_4 and 10 mL of *p*-anisaldehyde in 200 mL of 95% EtOH), or cerium sulfate (6.25 g of $(NH_4)_6Mo_7O_{24}$ and 1.5 g of $Ce(SO_4)_2$ in 250 mL of 10% aq H_2SO_4). Flash column chromatography was performed using Merck silica gel 60 (particle size 0.040–0.063 mm). NMR spectra were recorded using a Varian Mercury 300 MHz spectrometer or a Varian Unity Inova 500 MHz spectrometer. Chemical shifts were measured in parts per million and coupling constants in hertz, and the field is indicated in each case. The solvent peaks from $CDCl_3$ (7.26 ppm in ^{1}H NMR and 77.16 ppm in ^{13}C NMR) or CD_3OD (3.31 ppm in ^{1}H NMR) were used as standards. In case of diastereomeric mixtures, the following abbreviations are used; maj: major diastereomer, min: minor diastereomer, both: both diastereomers, one: one diastereomer. Elemental analyses were obtained from H. Kolbe, Mikroanalytisches Laboratorium, Mülheim/Ruhr, Germany. IR analysis was carried out on a Perkin–Elmer 1600 series FTIR spectrometer or on a Bruker Alpha FTIR spectrometer. Melting points were measured with a Buch & Holm melting point apparatus and are uncorrected. High-resolution LC-DAD-MS was performed on an Agilent 1100 system equipped with a photodiode array detector (DAD) and coupled to an LCT orthogonal time-of-flight mass spectrometer (Waters-Micromass) with a *Z*-spray electrospray ionization (ESI) source and a LockSpray probe (M+H 556.2771) and controlled by MassLynx 4.0 software.

*4.1.1. 4-(4-((tert-Butyldimethylsilyloxy)methyl)-1H-1,2,3-triazol-1-yl)butyl benzoate (**1**).* 4-Chlorobutyl benzoate (10.0 g, 47.1 mmol) and *n*-Bu_4NI (1.74 g, 4.71 mmol) were dissolved in anhydrous DMF (94 mL). NaN_3 (3.83 g, 58.9 mmol) was added cautiously. The solution was slowly heated to 60 °C and stirred for 23 h. The mixture was transferred to a separation funnel and diluted with Et_2O (600 mL). After washing with water (3×320 mL), the resulting organic phase was concentrated in vacuo to afford a yellow oil, which was used without further purification. The crude was dissolved in THF (422 mL) and DIPEA (12.1 mL, 70.6 mmol) was added followed by CuI (8.97 g, 47.1 mmol) and *tert*-butyldimethylsilyl propargyl ether (9.55 mL, 47.1 mmol). After stirring at 20 °C for 18 h, the yellow mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo giving a green oil. The residue was dissolved in EtOAc (500 mL) and washed with water (2×330 mL) and brine (330 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an oil, which was purified by flash column chromatography (MeOH/CH_2Cl_2 3:97) to give the triazole **1** (18.3 g, quantitative yield) as a yellow oil. R_f 0.60 (EtOAc/heptane 1:1); IR (neat, AgCl) ν 3428 (w), 3138 (m), 3069 (m), 2956 (s), 1719 (s), 1602 (m), 1585 (m), 1451 (s), 1389 (m), 1361 (m), 1271 (s), 1219 (m), 1176 (m), 1096 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04–8.01 (2H, m, *o*-Ph), 7.60–7.52 (2H, m, *p*-Ph, =CC*H*N), 7.47–7.42 (2H, m, *m*-Ph), 4.88 (2H, s, CH_2OSi), 4.46 (2H, t, *J* 7.1 Hz, CH_2N), 4.36 (2H, t, *J* 6.3 Hz, BzOCH_2), 2.15–2.05 (2H, m, CH_2CH$_2$N), 1.87–1.77 (2H, m, OCH$_2$CH_2), 0.91 (9H, s, SiCMe_3), 0.10 (6H, s, Me_2Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 149.0, 133.2, 130.1, 129.6 (2C), 128.5 (2C), 121.5, 64.0, 58.1, 49.9, 27.3, 26.0 (3C), 25.9, 18.4, −5.2 (2C); HRMS (ESI): *m*/*z* calcd for $C_{20}H_{31}N_3O_3Si$ $[M+H]^+$ 390.2213, found 390.2231.

*4.1.2. 4-(4-((tert-Butyldimethylsilyloxy)methyl)-1H-1,2,3-triazol-1-yl)-butan-1-ol (**2**).* A solution of the triazole **1** (1.98 g, 5.08 mmol) in anhydrous CH_2Cl_2 (49 mL) was cooled to −78 °C. DIBAL-H (1.0 M in hexane, 11.2 mL, 11.2 mmol) was added, and the mixture was stirred at −78 °C for 3 h. The reaction was quenched with MeOH (2.0 mL) and allowed to reach 20 °C. A satd aq solution of Rochelle's salt (60 mL), water (40 mL), and Et_2O (250 mL) were added, and the viscous mixture was stirred vigorously for 15 min. The mixture was transferred to a separatory funnel and the organic layer was isolated. The aqueous layer was extracted with EtOAc (3×80 mL) and the pooled organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to give a yellow oil. The product was purified by flash column chromatography (EtOAc/heptane 1:1 → EtOAc) to afford the alcohol **2** (1.31 g, 90%) as a colorless oil. R_f 0.10 (EtOAc/heptane 1:1); IR (neat, AgCl) ν 3372 (m), 2929 (s), 1734 (w), 1636 (w), 1559 (w), 1473 (m), 1257 (m), 1006 (s), 840 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, s, =C*H*N), 4.85 (2H, s, CH_2OSi), 4.41 (2H, t, *J* 7.1 Hz, CH_2N), 3.69 (2H, t, *J* 6.2 Hz, HOCH_2), 2.07–1.98 (2H, m, CH_2CH$_2$N), 1.81 (1H, br s, O*H*), 1.63–1.54 (2H, m, HOCH$_2$CH_2), 0.91 (9H, s, SiCMe_3), 0.10 (6H, s, Me_2Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 121.6, 61.9, 58.0, 50.2, 29.4, 27.1, 26.0 (3C), 18.5, −5.2 (2C). Anal. Calcd for $C_{13}H_{27}N_3O_2Si$: C, 54.70; H, 9.53; N, 14.72. Found: C, 54.63; H, 9.50; N, 14.81.

*4.1.3. 4-((tert-Butyldimethylsilyloxy)methyl)-1-(4-(tert-butyldiphenylsilyloxy)butyl)-1H-1,2,3-triazole (**3**).* The alcohol **2** (5.95 g, 20.9 mmol) was dissolved in anhydrous DMF (41.7 mL). Imidazole (2.84 g, 41.7 mmol) and TBDPSCl (8.13 mL, 31.3 mmol) were added. After stirring for 1 h at 20 °C, the mixture was diluted with EtOAc (140 mL) and then washed with water (70 mL) and brine (70 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:1) to give **3** (10.9 g, quantitative yield) as a colorless oil. R_f 0.85 (EtOAc/heptane 3:1); IR (neat) 3135 (w), 3071 (w), 3050 (w), 2998 (w), 2953 (m), 2930 (s), 2886 (m), 2857 (s), 1589 (w), 1471 (m), 1463 (m), 1428 (m), 1389 (m), 1361 (w), 1334 (w), 1308 (w), 1255 (m), 1218 (w), 1188 (w), 1134 (m), 1105 (s), 1088 (s), 1045 (m), 1022 (m), 1007 (m), 972 (w), 938 (w), 910 (w), 836 (m), 777 (m), 736 (m), 687 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66–7.63 (4H, m, *o*-Ph), 7.43–7.35 (7H, m, =C*H*N, *p*-Ph, *m*-Ph), 4.85 (2H, s, CH_2OSi), 4.34 (2H, t, *J* 7.2 Hz, CH_2N), 3.68 (2H, t, *J* 6.0 Hz, SiOCH_2CH$_2$), 2.06–1.96 (2H, m, CH_2CH$_2$N), 1.61–1.52 (2H, m, OCH$_2$CH_2), 1.04 (9H, s, Ph$_2$SiCMe_3), 0.91 (9H, s, Me$_2$SiCMe_3), 0.10 (6H, s, Me_2Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 135.7 (4C), 133.8 (2C), 129.8 (2C), 127.8 (4C), 121.4, 63.1, 58.1, 50.2, 29.4, 27.2, 27.0 (3C), 26.0 (3C), 19.3, 18.5, −5.1 (2C); HRMS (ESI): *m*/*z* calcd for $C_{29}H_{45}N_3O_2Si_2$ $[M+H]^+$ 524.3129, found 524.3159.

*4.1.4. (1-(4-(tert-Butyldiphenylsilyloxy)butyl)-1H-1,2,3-triazol-4-yl) methanol (**4**).* The disilylprotected compound **3** (10.9 g, 20.9 mmol) was dissolved in MeOH (350 mL). PPTS (262 mg, 1.04 mmol) was added, and the solution was heated to 55 °C. After stirring for 23 h, the solvent was removed in vacuo. The residue was redissolved in EtOAc (420 mL) and washed with brine (420 mL) and water (420 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 3:7 → EtOAc) to give the alcohol **4** (6.54 g, 77%) as white crystals. R_f 0.39 (EtOAc/heptane 3:1); mp 111–112 °C; IR (neat) ν 3232 (s), 3126 (m), 2927 (s), 2854 (m), 1472 (w), 1427 (m), 1359 (w), 1225 (w), 1145 (w), 1109 (s), 1081 (s), 1020

(m), 980 (m), 817 (w), 708 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65–7.62 (4H, m, *o*-Ph), 7.47 (1H, s, =C*H*N), 7.43–7.35 (6H, m, *p*-Ph, *m*-Ph), 4.79 (2H, d, *J* 6.1 Hz, CH_2OH), 4.35 (2H, t, *J* 7.2 Hz, CH_2N), 3.68 (2H, t, *J* 6.0 Hz, SiOCH_2), 2.23 (1H, t, *J* 6.1 Hz, O*H*), 2.07–1.97 (2H, m, CH_2CH$_2$N), 1.63–1.52 (2H, m, OCH$_2$CH_2), 1.04 (9H, s, SiCMe_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 135.6 (4C), 133.7 (2C), 129.8 (2C), 127.8 (4C), 121.7, 63.0, 56.3, 50.3, 29.4, 27.0, 27.0 (3C), 19.3. Anal. Calcd for $C_{23}H_{31}N_3O_2Si$: C, 67.44; H, 7.63; N, 10.26. Found: C, 67.52; H, 7.59; N, 10.22.

*4.1.5. (±)-1-(tert-Butyldimethylsilyloxy)-2-methylbut-3-en-2-ol (**5**).* 1-(*tert*-Butyldimethylsilyloxy)propan-2-one (12 mL, 62.2 mmol) was dissolved in anhydrous THF (114 mL). The mixture was stirred at 0 °C, and vinyl magnesium chloride (1.6 M in THF, 47 mL, 74.6 mmol) was added dropwise over 20 min. The cooling bath was removed and after 2 h, the reaction mixture was diluted with Et_2O (480 mL) and washed with satd aq NH_4Cl (290 mL) and water (290 mL). The combined aqueous phases were extracted with Et_2O (200 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to give **5** as a colorless oil (10.4 g, 78%), which was used without further purification. R_f 0.63 (EtOAc/heptane 1:1); IR (neat, AgCl) ν 3447 (br), 3088 (w), 2931 (s), 1718 (w), 1653 (w), 1472 (m), 1362 (m), 1257 (m), 1100 (s), 1006 (m), 922 (m), 838 (s), 778 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (1H, dd, *J* 17.4, 10.8 Hz, C*H*=CH$_a$H$_b$), 5.29 (1H, dd, *J* 17.4, 1.4 Hz, CH=C*H*$_a$H$_b$), 5.11 (1H, dd, *J* 10.8, 1.4 Hz, CH=CH$_a$*H*$_b$), 3.47 (1H, d, *J* 9.5 Hz, C*H*$_a$H$_b$), 3.42 (1H, d, *J* 9.5 Hz, CH$_a$*H*$_b$), 1.23 (3H, s, *Me*), 0.90 (9H, s, SiC*Me*$_3$), 0.06 (3H, s, *Me*Si), 0.06 (3H, s, *Me*Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 113.6, 73.1, 70.4, 26.0 (3C), 23.9, 18.5, −5.2, −5.3.

*4.1.6. (±)-(E)-Methyl 5-(tert-butyldimethylsilyloxy)-4-hydroxy-4-methylpent-2-enoate (**6**).* Alcohol **5** (8.40 g, 38.8 mmol) was dissolved in anhydrous CH_2Cl_2 (400 mL) and methyl acrylate (69.5 mL, 776 mmol) was added. Hoveyda–Grubbs second generation catalyst (0.12 g, 0.20 mmol) was added, and the mixture was heated to reflux. After stirring for 48 h, the mixture was concentrated in vacuo to give a green semisolid, which was recrystallized from EtOAc/heptane, and a crystalline by-product was filtered off. The filtrate was concentrated in vacuo to give a green oil. The crude product was purified by flash column chromatography (EtOAc/heptane 1:7) to afford the methyl ester **6** (9.31 g, 88%) as a pale yellow oil. R_f 0.30 (EtOAc/heptane 1:4); IR (neat, AgCl) ν 3482 (br), 2954 (s), 2858 (s), 1728 (s), 1662 (m), 1472 (m), 1437 (m), 1363 (m), 1259 (s), 1100 (s), 981 (m), 838 (s), 778 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (1H, d, *J* 15.7 Hz, COCH=C*H*), 6.10 (1H, d, *J* 15.7 Hz, COC*H*=CH), 3.74 (3H, s, O*Me*), 3.53 (1H, d, *J* 9.6 Hz, C*H*$_a$H$_b$), 3.48 (1H, d, *J* 9.6 Hz, CH$_a$*H*$_b$), 1.26 (3H, s, *Me*), 0.88 (9H, s, SiC*Me*$_3$), 0.06 (3H, s, *Me*Si), 0.04 (3H, s, *Me*Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 152.1, 119.9, 73.1, 69.8, 51.7, 25.9 (3C), 23.6, 18.4, −5.3, −5.4; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{26}O_4Si$ $[M+H]^+$ 275.1679, found 275.1680.

*4.1.7. (±)-(E)-Methyl 5-(tert-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate (**7**).* The methyl ester **6** (4.16 g, 15.2 mmol) and PMBTCA[22] (8.14 g, 30.3 mmol) were dissolved in anhydrous toluene (125 mL), and La(OTf)$_3$ (622 mg, 1.06 mmol) was added. After stirring at 20 °C for 16 h, the mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo to give a yellowish oil, which was purified by flash column chromatography (EtOAc/toluene/heptane 1:50:50) to give the PMB-protected methyl ester **7** (5.07 g, 85%) as a colorless oil. R_f 0.73 (toluene/heptane 1:4); IR (neat, AgCl) ν 2952 (s), 2856 (s), 2061 (w), 1883 (w), 1726 (s), 1658 (m), 1613 (m), 1587 (m), 1515 (s), 1465 (m), 1382 (m), 1250 (s), 1113 (s), 939 (m), 840 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* 8.6 Hz, *o*-Ar), 6.99 (1H, d, *J* 16.0 Hz, COCH=C*H*), 6.88 (2H, d, *J* 8.6 Hz, *m*-Ar), 6.06 (1H, d, *J* 16.0 Hz, COC*H*=CH), 4.44 (1H, d, *J* 10.7 Hz, C*H*$_a$H$_b$Ar), 4.38 (1H, d, *J* 10.7 Hz, CH$_a$*H*$_b$Ar), 3.81 (3H, s, BnO*Me*), 3.77 (3H, s, COO*Me*), 3.63 (2H, s, CH_2OSi), 1.41 (3H, s, *Me*), 0.89 (9H, s, SiC*Me*$_3$), 0.05 (3H, s, *Me*Si), 0.04 (3H, s, *Me*Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 159.1, 151.2, 131.1, 129.1 (2C), 121.6, 113.9 (2C), 78.3, 69.0, 65.3, 55.4, 51.8, 25.9 (3C), 20.3, 18.3, −5.3 (2C); HRMS (ESI): *m*/*z* calcd for $C_{21}H_{34}O_5Si$ $[M+Na]^+$ 417.2073, found 417.2073.

*4.1.8. (±)-(E)-5-(tert-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-methylpent-2-enoic acid (**8**).* The methyl ester **7** (3.47 g, 8.79 mmol) was dissolved in THF (132 mL) and cooled to 0 °C. A solution of LiOH (631 mg, 26.4 mmol) in H_2O (44 mL) was added, and the resulting mixture was stirred at 20 °C. After 46 h, the reaction was quenched with satd aq NaH_2PO_4 (100 mL), and EtOAc (100 mL) was added. The organic phase was isolated, and the aqueous phase was extracted with EtOAc (3×100 mL). The pooled organic phases were washed with water (200 mL) and brine (200 mL). Subsequently, they were dried ($MgSO_4$), filtered and, concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane/AcOH 9:90:1) to afford the carboxylic acid **8** (2.97 g, 89%) as a white solid. R_f 0.60 (EtOAc/heptane/AcOH 70:30:1); mp 68–71 °C; IR (neat) ν 2927 (br), 1880 (w), 1698 (s), 1652 (m), 1614 (m), 1587 (m), 1515 (s), 1463 (m), 1373 (m), 1254 (s), 939 (m), 845 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* 8.6 Hz, *o*-Ar), 7.09 (1H, d, *J* 16.0 Hz, COCH=C*H*), 6.87 (2H, d, *J* 8.6 Hz, *m*-Ar), 6.06 (1H, d, *J* 16.0 Hz, COC*H*=CH), 4.44 (1H, d, *J* 10.7 Hz, C*H*$_a$H$_b$Ar), 4.38 (1H, d, *J* 10.7 Hz, CH$_a$*H*$_b$Ar), 3.80 (3H, s, O*Me*), 3.63 (2H, s, CH_2OSi), 1.42 (3H, s, *Me*), 0.88 (9H, s, SiC*Me*$_3$), 0.04 (3H, s, *Me*Si), 0.03 (3H, s, *Me*Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 159.1, 153.8, 131.0, 129.1 (2C), 121.4, 113.9 (2C), 78.3, 68.9, 65.4, 55.4, 25.9 (3C), 20.3, 18.3, −5.3 (2C). Anal. Calcd for $C_{20}H_{32}O_5Si$: C, 63.12; H, 8.48. Found: C, 63.20; H, 8.36.

*4.1.9. (±)-(E)-5-(tert-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-methylpent-2-en-1-ol (**9**).* The methyl ester **7** (703 mg, 1.78 mmol) was dissolved in anhydrous CH_2Cl_2 (16 mL) and cooled to −78 °C. DIBAL-H (1.0 M in hexanes, 3.92 mL, 3.92 mmol) was added, and the mixture was stirred at −78 °C for 3 h. The reaction was quenched with MeOH (1.0 mL) and the cold bath was removed. At 20 °C, a satd aq solution of Rochelle's salt (20 mL), water (10 mL), and Et_2O (100 mL) was added, and the viscous mixture was stirred vigorously for 15 min. The organic phase was isolated, and the aqueous phase was extracted with EtOAc (3×50 mL). The pooled organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to give a yellow oil. The oil was purified by flash column chromatography (EtOAc/heptane 1:2) to afford the alcohol **9** (583 mg, 89%) as a colorless oil. R_f 0.87 (MeOH/EtOAc 1:99); IR (neat, AgCl) ν 3418 (br), 2930 (s), 1740 (m), 1613 (m), 1587 (m), 1514 (s), 1464 (m), 1379 (m), 1250 (s), 1172 (m), 1110 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* 8.5 Hz, *o*-Ar), 6.86 (2H, d, *J* 8.5 Hz, *m*-Ar), 5.88 (1H, dt, *J* 16.2, 5.3 Hz, CH$_2$C*H*=CH), 5.74 (1H, d, *J* 16.2 Hz, CH$_2$CH=C*H*), 4.39 (2H, s, CH_2Ar), 4.19 (2H, dd, *J* 5.3, 1.0 Hz, CH_2CH=CH), 3.79 (3H, s, O*Me*), 3.59 (1H, d, *J* 9.9 Hz, C*H*$_a$H$_b$OSi), 3.55 (1H, d, *J* 9.9 Hz, CH$_a$*H*$_b$OSi), 1.36 (3H, s, *Me*), 0.89 (9H, s, SiC*Me*$_3$), 0.04 (3H, s, *Me*Si), 0.03 (3H, s, *Me*Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 134.5, 131.8, 130.7, 129.0 (2C), 113.8 (2C), 78.0, 69.6, 64.7, 63.6, 55.4, 26.0 (3C), 20.3, 18.4, −5.2, −5.2. Anal. Calcd for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.35. Found: C, 65.45; H, 9.31.

*4.1.10. (±)-(E)-4-(4-Methoxybenzyloxy)-4-methylpent-2-en-1,5-diol (**10**).* The alcohol **9** (8.80 g, 24.0 mmol) was dissolved in anhydrous THF (59 mL) and TBAF (1.0 M in THF, 36.0 mL, 36.0 mmol) was added dropwise. After stirring for 19 h, the mixture was diluted with EtOAc (150 mL) and washed with satd aq NH_4Cl (120 mL) and water (2×120 mL). The combined aqueous phases were extracted with EtOAc (2×120 mL). The combined organic phases were dried

($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:1→MeOH/EtOAc 1:99) giving the diol **10** (6.06 g, quantitative yield) as a colorless oil, which crystallizes upon storage at 5 °C to give a white solid. R_f 0.54 (MeOH/EtOAc 1:99); mp 44–45 °C; IR (neat, AgCl) ν 3379 (br), 2935 (s), 1613 (m), 1586 (m), 1514 (s), 1465 (m), 1381 (m), 1302 (m), 1248 (s), 1173 (m), 1112 (m), 1036 (s), 981 (m), 913 (w), 891 (w), 822 (m), 733 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* 8.6 Hz, *o*-Ar), 6.87 (2H, d, *J* 8.6 Hz, *m*-Ar), 5.91 (1H, dt, 16.1, 5.2 Hz, CH_2CH=CH), 5.78 (1H, d, *J* 16.1 Hz, CH_2CH=C*H*), 4.33 (2H, s, CH_2Ar), 4.19 (2H, d, *J* 5.2 Hz, CH_2CH=CH), 3.80 (3H, s, O*Me*), 3.50 (2H, s, CH_2OSi), 2.08 (2H, br s, 2×O*H*), 1.38 (3H, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 132.9, 131.8, 131.1, 129.2 (2C), 113.9 (2C), 77.9, 69.7, 64.6, 63.0, 55.4, 19.3; HRMS (ESI): *m*/*z* calcd for $C_{14}H_{20}O_4$ $[M+Na]^+$ 275.1259, found 275.1255.

*4.1.11. (±)-(E)-5-(tert-Butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)-2-methylpent-3-en-1-ol (**11**).* The diol **10** (1.41 g, 5.60 mmol) was dissolved in anhydrous CH_2Cl_2 (65 mL) and imidazole (539 mg, 8.41 mmol) was added. The mixture was cooled to −78 °C, and a solution of TBDPSCl (1.46 mL, 5.60 mmol) in anhydrous CH_2Cl_2 (10 mL) was added over 5 min. After 3 h, the mixture was diluted with CH_2Cl_2 (60 mL) and washed with brine (40 mL) and water (40 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/heptane 1:2) affording the TBDPS-protected alcohol **11** (2.75 g, quantitative yield) as a colorless oil. R_f 0.30 (EtOAc/heptane 1:2); IR (neat, AgCl) ν 3457 (br), 2932 (s), 1613 (m), 1588 (m), 1514 (s), 1473 (m), 1428 (m), 1380 (m), 1302 (m), 1249 (s), 1173 (m), 1112 (s), 978 (m), 823 (m), 741 (m), 702 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70–7.66 (4H, m, *o*-Ph), 7.45–7.33 (6H, m, *p*-Ph, *m*-Ph), 7.23 (2H, d, *J* 8.5 Hz, *o*-Ar), 6.86 (2H, d, *J* 8.5 Hz, *m*-Ar), 5.81–5.80 (2H, m, C*H*=C*H*), 4.29–4.28 (4H, m, CH_2Ar, CH_2CH=), 3.80 (3H, s, O*Me*), 3.52 (1H, d, *J* 10.9 Hz, C$H_a$$H_b$OSi), 3.41 (1H, d, *J* 10.9 Hz, C$H_a$$H_b$OSi), 1.98 (1H, br s, OH), 1.36 (3H, s, *Me*), 1.07 (9H, s, SiCMe_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 135.6 (4C), 133.7, 133.7, 131.9, 131.5, 131.2, 129.8 (2C), 129.3 (2C), 127.8 (4C), 113.9 (2C), 77.9, 69.8, 64.7, 64.1, 55.4, 27.0 (3C), 19.4, 19.3. Anal. Calcd for $C_{30}H_{38}O_4Si$: C, 73.43; H, 7.81. Found: C, 73.27; H, 7.75.

*4.1.12. (±)-(E)-5-(tert-Butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)-2-methylpent-3-enoic acid (**12**).* Anhydrous CH_2Cl_2 (220 mL) and DMSO (5.79 mL, 81.7 mmol) were mixed and cooled to −78 °C. Oxalyl chloride (3.45 mL, 40.8 mmol) was added dropwise, followed by dropwise addition of a solution of the alcohol **11** (10.0 g, 20.4 mmol) in anhydrous CH_2Cl_2 (110 mL). After 30 min, anhydrous Et_3N (28.5 mL, 204 mmol) was added. After further 15 min, the mixture was allowed to reach 20 °C and then diluted with CH_2Cl_2 (600 mL) and washed with satd aq NH_4Cl (400 mL) and water (400 mL) The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude aldehyde, which was used without further purification. The crude aldehyde was dissolved in THF (120 mL). *t*-BuOH (240 mL) and 2-methyl-2-butene (86 mL, 811 mmol) were added followed by a solution of $NaClO_2$ (23.3 g, 257 mmol) and NaH_2PO_4 (30.9 g, 257 mmol) in water (160 mL). After 1½ hours, the mixture was diluted with satd aq NaH_2PO_4 (500 mL) and stirred for 15 min. Subsequently, the mixture was extracted with EtOAc (3×500 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane/AcOH 66:33:1) to afford the carboxylic acid **12** (9.89 g, 96%) as a colorless oil. R_f 0.25 (MeOH/toluene 5:95); IR (neat) ν 3071 (m), 3049 (m), 2997 (m), 2956 (m), 2931 (m), 2893 (m), 2857 (m), 1712 (m), 1613 (m), 1588 (w), 1513 (m), 1462 (m), 1428 (m), 1380 (m), 1302 (m), 1247 (s), 1202 (m), 1174 (m), 1107 (s), 1028 (m), 998 (m), 971 (m), 939 (m), 909 (m), 821 (m), 735 (m), 700 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68–7.65 (4H, m, *o*-Ph), 7.42–7.34 (6H, m, *p*-Ph, *m*-Ph), 7.25 (2H, d, *J* 8.7 Hz, *o*-Ar), 6.89 (2H, d, *J* 8.7 Hz, *m*-Ar), 6.01 (1H, dt, *J* 15.7, 3.4 Hz, CH_2CH=CH), 5.92 (1H, m, CH_2CH=C*H*), 4.43 (1H, d, *J* 10.5 Hz, C$H_a$$H_b$Ar), 4.38 (1H, d, *J* 10.5 Hz, C$H_a$$H_b$Ar), 4.29 (2H, dd, *J* 3.4, 1.1 Hz, CH_2CH=CH), 3.82 (3H, s, O*Me*), 1.65 (3H, s, CH_3), 1.07 (9H, s, SiCMe_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 159.5, 135.6 (4C), 133.5, 133.2 (2C), 129.9 (2C), 129.8, 129.6 (2C), 128.1, 127.9 (4C), 114.0 (2C), 80.2, 66.5, 63.6, 55.4, 26.9 (3C), 22.1, 19.4. Anal. Calcd for $C_{30}H_{36}O_5Si$: C, 71.39; H, 7.19. Found: C, 70.67; H, 7.17.

4.2. Representative procedure for the preparation of esters (13, 15, 17, 19)

*4.2.1. (±)-(E)-4-(4-((tert-Butyldimethylsilyloxy)methyl)-1H-1,2,3-triazol-1-yl)butyl 5-(tert-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate (**13**).* The carboxylic acid **8** (624 mg, 1.64 mmol) and the alcohol **2** (515 mg, 1.80 mmol) were dissolved in anhydrous CH_2Cl_2 (25 mL) and DMAP (40 mg, 0.33 mmol) and EDC·HCl (472 mg, 2.46 mmol) were added. The reaction was stirred for 18 h at 20 °C and then concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane 1:2) to afford the ester **13** (930 mg, 87%) as a colorless oil. R_f 0.31 (MeOH/toluene 5:95); IR (neat, AgCl) ν 2927 (s), 1734 (s), 1653 (m), 1613 (m), 1516 (m), 1472 (m), 1374 (m), 1249 (s), 1104 (s), 939 (w), 839 (m), 779 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (1H, s, =C*H*N), 7.25 (2H, d, *J* 8.4 Hz, *o*-Ar), 6.97 (1H, d, *J* 16.0 Hz, COCH=C*H*), 6.86 (2H, d, *J* 8.4 Hz, *m*-Ar), 6.02 (1H, d, *J* 16.0 Hz, COC*H*=CH), 4.84 (2H, s, =CCH_2OSi), 4.42 (1H, d, *J* 11.1 Hz, C$H_a$$H_b$Ar), 4.38 (2H, t, *J* 7.4 Hz, CH_2N), 4.37 (1H, d, *J* 11.1 Hz, C$H_a$$H_b$Ar), 4.18 (2H, t, *J* 6.3 Hz, OC$H_2$$CH_2$), 3.79 (3H, s, O*Me*), 3.61 (2H, s, C(OPMB)CH_2OSi), 2.05–1.95 (2H, m, C$H_2$$CH_2$N), 1.76–1.65 (2H, m, HOCH_2CH_2), 1.40 (3H, s, *Me*), 0.91 (9H, s, SiCMe_3), 0.87 (9H, s, SiCMe_3), 0.09 (6H, s, Me_2Si), 0.02 (3H, s, *Me*Si), 0.01 (3H, s, *Me*Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 159.1, 151.5, 148.9, 131.1, 129.0 (2C), 121.6, 121.5, 113.9 (2C), 78.3, 68.9, 65.3, 63.5, 58.1, 55.4, 49.9, 27.2, 26.0 (3C), 25.9 (3C), 25.9, 20.2, 18.5, 18.3, −5.1 (2C), −5.3 (2C).

*4.2.2. (±)-(E)-(1-(4-(tert-Butyldiphenylsilyloxy)butyl)-1H-1,2,3-triazol-4-yl)methyl 5-(tert-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate (**15**).* Colorless oil, 87% yield. R_f 0.40 (MeOH/toluene 5:95); IR (neat) ν 3139 (w), 3071 (w), 3048 (w), 2998 (w), 2954 (s), 2930 (s), 2894 (m), 2857 (s), 1720 (s), 1656 (w), 1613 (w), 1588 (w), 1514 (m), 1463 (m), 1442 (m), 1428 (m), 1387 (m), 1361 (w), 1301 (m), 1249 (s), 1169 (m), 1105 (s), 1033 (m), 1007 (m), 938 (w), 910 (w), 836 (s), 823 (m), 777 (m), 731 (m), 701 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65–7.62 (4H, m, *o*-Ph), 7.56 (1H, s, =C*H*N), 7.45–7.36 (6H, m, *p*-Ph, *m*-Ph), 7.23 (2H, d, *J* 8.5 Hz, *o*-Ar), 7.00 (1H, d, *J* 16.1 Hz, COCH=C*H*), 6.85 (2H, d, *J* 8.5 Hz, *m*-Ar), 6.05 (1H, d, *J* 16.1 Hz, COC*H*=CH), 5.30 (2H, s, CH_2OCO), 4.46–4.32 (4H, m, CH_2Ar, CH_2N), 3.79 (3H, s, O*Me*), 3.68 (2H, t, *J* 6.0 Hz, SiOC$H_2$$CH_2$), 3.60 (2H, s, C(OPMB)C$H_2$OSi), 2.07–1.97 (2H, m, C$H_2$$CH_2$N), 1.61–1.52 (2H, m, SiOCH_2CH_2), 1.38 (3H, s, *Me*), 1.04 (9H, s, Ph_2SiCMe_3), 0.86 (9H, s, Me_2SiCMe_3), 0.01 (3H, s, *Me*Si), 0.00 (3H, s, *Me*Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 164.4, 157.3, 148.2, 141.0 (4C), 139.0 (2C), 136.4, 135.2 (2C), 134.4 (2C), 133.2 (4C), 129.1, 126.7, 119.2 (2C), 83.6, 74.3, 70.6, 68.4, 63.2, 60.7, 55.7, 34.7, 32.4, 32.3 (3C), 31.3 (3C), 25.6, 24.7, 23.7, 0.0, 0.0; HRMS (ESI): *m*/*z* calcd for $C_{43}H_{61}N_3O_6Si_2$ $[M+H]^+$ 772.4177, found 772.4179.

*4.2.3. (±)-(E)-(1-(4-(tert-Butyldiphenylsilyloxy)butyl)-1H-1,2,3-triazol-4-yl)methyl 5-(tert-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)-2-methylpent-3-enoate (**17**).* Colorless oil, 58% yield. R_f 0.40 (MeOH/toluene 5:95); IR (neat) ν 3136 (w), 3071 (w), 3048 (w), 3013 (w), 2998 (w), 2955 (m), 2931 (m), 2892 (m), 2857 (m), 1736 (m), 1613 (w), 1588 (w), 1514 (m), 1471 (m), 1462 (m), 1427 (m),

1387 (m), 1362 (w), 1302 (w), 1248 (m), 1174 (m), 1105 (s), 1047 (m), 1032 (m), 998 (m), 968 (m), 939 (w), 910 (w), 822 (m), 735 (m), 700 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67–7.62 (8H, m, *o*-Ph), 7.48 (1H, s, =C*H*N), 7.44–7.32 (12H, m, *p*-Ph, *m*-Ph), 7.26 (2H, d, *J* 8.7 Hz, *o*-Ar), 6.84 (2H, d, *J* 8.7 Hz, *m*-Ar), 6.03 (1H, dt, *J* 15.7, 1.6 Hz, CH_2CH=C*H*), 5.91 (1H, dt, *J* 15.7, 4.0 Hz, CH_2CH=CH), 5.31 (2H, s, CH_2OCO), 4.42 (1H, d, *J* 10.6 Hz, CH_aH_bAr), 4.36 (1H, d, *J* 10.6 Hz, CH_aH_bAr), 4.28 (2H, t, *J* 7.3 Hz, NCH_2), 4.24 (2H, dd, *J* 4.0, 1.6 Hz, CH_2CH=CH), 3.78 (3H, s, O*Me*), 3.66 (2H, t, *J* 6.0 Hz, CH_2CH_2O), 2.01–1.91 (2H, m, NCH_2CH_2), 1.56 (3H, s, *Me*), 1.55–1.48 (2H, m, CH_2CH_2O), 1.05 (9H, s, $SiCMe_3$), 1.04 (9H, s, $SiCMe_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 159.2, 142.7, 135.6 (4C), 135.6 (4C), 133.7 (2C), 133.6 (2C), 131.6, 130.7, 129.8 (4C), 129.4, 129.4 (2C), 127.8 (4C), 127.8 (4C), 123.7, 113.8 (2C), 80.1, 66.9, 63.8, 63.0, 58.6, 55.4, 50.3, 29.4, 27.0, 27.0 (3C), 26.9 (3C), 24.2, 19.4, 19.3; HRMS (ESI): *m*/*z* calcd for $C_{53}H_{65}N_3O_6Si_2$ $[M+H]^+$ 896.4490, found 896.4462.

*4.2.4. (±)-(E)-4-(4-((tert-Butyldimethylsilyloxy)methyl)-1H-1,2,3-triazol-1-yl)butyl 5-(tert-butyldiphenylsilyloxy)-2-(4-methoxybenzyl oxy)-2-methylpent-3-enoate (**19**).* Colorless oil, 71% yield. R_f 0.31 (MeOH/toluene 5:95); IR (neat) ν 3136 (w), 3071 (w), 3048 (w), 2997 (w), 2954 (m), 2931 (s), 2893 (m), 2856 (m), 1734 (m), 1613 (m), 1588 (w), 1514 (m), 1462 (m), 1428 (m), 1381 (m), 1362 (m), 1301 (m), 1247 (s), 1174 (m), 1105 (s), 1043 (m), 970 (m), 939 (w), 836 (m), 777 (m), 740 (m), 701 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68–7.64 (4H, m, *o*-Ph), 7.42–7.33 (7H, m, =C*H*N, *p*-Ph, *m*-Ph), 7.28 (2H, d, *J* 8.6 Hz, *o*-Ar), 6.85 (2H, d, *J* 8.6 Hz, *m*-Ar), 6.04 (1H, dt, *J* 15.7, 1.5 Hz, CH_2CH=C*H*), 5.92 (1H, dt, *J* 15.7, 3.8 Hz, CH_2CH=CH), 4.83 (2H, s, =CCH_2O), 4.44 (1H, d, *J* 10.8 Hz, CH_aH_bAr), 4.38 (1H, d, *J* 10.8 Hz, CH_aH_bAr), 4.31 (2H, t, *J* 7.0 Hz, CH_2N), 4.26 (2H, dd, *J* 3.9, 1.5 Hz, CH_2CH=CH), 4.18 (2H, t, *J* 6.4 Hz, OCH_2CH_2), 3.79 (3H, s, O*Me*), 2.01–1.90 (2H, m, CH_2CH_2N), 1.73–1.60 (2H, m, OCH_2CH_2), 1.58 (3H, s, *Me*), 1.06 (9H, s, Ph_2SiCMe_3), 0.91 (9H, s, Me_2SiCMe_3), 0.09 (6H, s, Me_2Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 159.2, 148.8, 135.6 (4C), 133.6 (2C), 131.5, 130.8, 129.9 (2C), 129.6, 129.2 (2C), 127.8 (4C), 121.5, 113.8 (2C), 80.2, 66.8, 64.3, 63.8, 58.1, 55.4, 49.7, 27.1, 26.9 (3C), 26.0 (3C), 25.7, 24.0, 19.4, 18.5, −5.1 (2C); HRMS (ESI): *m*/*z* calcd for $C_{43}H_{61}N_3O_6Si_2$ $[M+H]^+$ 772.4177, found 772.4214.

4.3. Representative procedure for the preparation of diols (14, 16, 18, 20)

*4.3.1. (±)-(E)-4-(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)butyl 5-hydroxy-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate (**14**).* The ester **13** (2.03 g, 3.14 mmol) was dissolved in anhydrous THF (27.7 mL) and TBAF (1.0 M in THF, 9.42 mL, 9.42 mmol) was added dropwise. The mixture was stirred for 4½ h and then diluted with EtOAc (140 mL), washed with satd aq NH_4Cl (80 mL) and water (2×80 mL). The combined aqueous phases were extracted with EtOAc (2×80 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (MeOH/EtOAc 1:99→5:95) to afford the diol **14** (1.13 g, 86%) as a colorless oil. R_f 0.10 (MeOH/EtOAc 1:99); IR (neat) ν 3374 (br), 3142 (m), 2938 (m), 2873 (m), 2839 (m), 1712 (s), 1654 (m), 1612 (m), 1513 (m), 1462 (m), 1443 (m), 1383 (m), 1301 (m), 1247 (s), 1171 (m), 1110 (m), 1031 (s), 895 (w), 821 (m), 778 (w), 754 (w), 726 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (1H, s, =C*H*N), 7.25 (2H, d, *J* 8.8 Hz, *o*-Ar), 6.97 (1H, d, *J* 16.1 Hz, COCH=C*H*), 6.88 (2H, d, *J* 8.8 Hz, *m*-Ar), 6.04 (1H, d, *J* 16.1 Hz, COC*H*=CH), 4.77 (2H, s, =CCH_2OH), 4.40 (2H, t, *J* 7.1 Hz, CH_2N), 4.39 (1H, d, *J* 10.6 Hz, CH_aH_bAr), 4.32 (1H, d, *J* 10.6 Hz, CH_aH_bAr), 4.17 (2H, t, *J* 6.3 Hz, OCH_2CH_2), 3.80 (3H, s, O*Me*), 3.60 (1H, d, *J* 11.5 Hz, C(OPMB)CH_aH_bOH), 3.55 (1H, d, *J* 11.5 Hz, C(OPMB)CH_aH_bOH), 2.07–1.97 (2H, m, CH_2CH_2N), 1.75–1.66 (2H, m, OCH_2CH_2), 1.42 (3H, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 159.3, 150.0, 147.9, 130.4, 129.3 (2C), 122.5, 121.8, 114.0 (2C), 78.1, 68.9, 65.3, 63.7, 56.7, 55.4, 49.9, 27.1, 25.7, 19.3. Anal. Calcd for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 60.02; H, 7.06; N, 9.88.

*4.3.2. (±)-(E)-(1-(4-Hydroxybutyl)-1H-1,2,3-triazol-4-yl)methyl 5-hydroxy-4-(4-methoxybenzyloxy)-4-methylpent-2-enoate (**16**).* White solid, 78% yield. R_f 0.15 (MeOH/EtOAc 1:99); mp 70–71 °C; IR (neat) ν 3332 (br), 3120 (m), 3072 (w), 3034 (w), 2935 (m), 2870 (m), 2838 (m), 1716 (s), 1655 (m), 1612 (m), 1586 (w), 1513 (m), 1462 (m), 1442 (m), 1381 (m), 1316 (m), 1301 (m), 1249 (m), 1218 (m), 1171 (s), 1108 (m), 1046 (s), 1007 (m), 973 (m), 942 (w), 900 (w), 871 (m), 827 (m), 815 (m), 781 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (1H, s, =C*H*N), 7.24 (2H, d, *J* 8.7 Hz, *o*-Ar), 7.00 (1H, d, *J* 16.1 Hz, COCH=C*H*), 6.87 (2H, d, *J* 8.7 Hz, *m*-Ar), 6.07 (1H, d, *J* 16.1 Hz, COC*H*=CH), 5.30 (2H, s, CH_2OCO), 4.41 (2H, t, *J* 7.1 Hz, CH_2N), 4.37 (1H, d, *J* 10.4 Hz, CH_aH_bAr), 4.31 (1H, d, *J* 10.4 Hz, CH_aH_bAr), 3.80 (3H, s, O*Me*), 3.67 (2H, t, *J* 6.2 Hz, CH_2CH_2OH), 3.57 (1H, d, *J* 11.5 Hz, C(OPMB)CH_aH_bOH), 3.52 (1H, d, *J* 11.5 Hz, C(OPMB)CH_aH_bOH), 2.07–1.97 (2H, m, NCH_2CH_2), 1.62–1.53 (2H, m, CH_2CH_2OH), 1.41 (3H, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 159.3, 150.4, 142.7, 130.4, 129.2 (2C), 124.1, 122.2, 114.0 (2C), 78.1, 68.8, 65.2, 61.9, 57.8, 55.4, 50.3, 29.3, 27.0, 19.3. Anal. Calcd for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 60.04; H, 7.08; N, 9.94.

*4.3.3. (±)-(E)-(1-(4-Hydroxybutyl)-1H-1,2,3-triazol-4-yl)methyl 5-hydroxy-2-(4-methoxybenzyloxy)-2-methylpent-3-enoate (**18**).* Colorless oil, 76% yield. R_f 0.15 (MeOH/EtOAc 1:99); IR (neat) ν 3362 (br), 3143 (m), 3042 (w), 2937 (m), 2870 (m), 2839 (m), 1732 (s), 1612 (m), 1586 (w), 1513 (s), 1456 (m), 1443 (m), 1381 (m), 1302 (m), 1245 (s), 1175 (m), 1107 (s), 1084 (m), 1051 (m), 1027 (s), 968 (m), 821 (m), 784 (w), 755 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (1H, s, =C*H*N), 7.27 (2H, d, *J* 8.8 Hz, *o*-Ar), 6.85 (2H, d, *J* 8.8 Hz, *m*-Ar), 5.96 (1H, dt, *J* 15.8, 4.4 Hz, CH_2CH=CH), 5.87 (1H, d, *J* 15.8 Hz, CH_2CH=C*H*), 5.35 (1H, d, *J* 12.7 Hz, CH_aH_bOCO), 5.29 (1H, d, *J* 12.7 Hz, CH_aH_bOCO), 4.44 (1H, d, *J* 10.4 Hz, CH_aH_bAr), 4.39 (2H, t, *J* 7.0 Hz, NCH_2), 4.37 (1H, d, *J* 10.4 Hz, CH_aH_bAr), 4.15 (2H, dd, *J* 4.4, 0.9 Hz, CH_2CH=CH), 3.79 (3H, s, O*Me*), 3.63 (2H, t, *J* 6.2 Hz, CH_2CH_2OH), 2.08–1.93 (2H, m, NCH_2CH_2), 1.60 (3H, s, *Me*), 1.57–1.48 (2H, m, CH_2CH_2OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 159.2, 142.5, 131.9, 130.6, 130.5, 129.4 (2C), 123.9, 113.8 (2C), 80.0, 66.8, 62.5, 61.7, 58.4, 55.4, 50.3, 29.3, 26.9, 23.1. Anal. Calcd for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 60.45; H, 7.06; N, 10.08.

*4.3.4. (±)-(E)-4-(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)butyl 5-hydroxy-2-(4-methoxybenzyloxy)-2-methylpent-3-enoate (**20**).* Colorless oil, 93% yield. R_f 0.10 (MeOH/EtOAc 1:99); IR(neat) ν 3360 (br), 3144 (m), 2961 (m), 2936 (m), 2872 (m), 2839 (m), 1730 (s), 1668 (w), 1613 (m), 1586 (w), 1553 (w), 1513 (s), 1457 (m), 1382 (m), 1301 (m), 1246 (s), 1175 (m), 1112 (m), 1084 (m), 1031 (s), 979 (m), 880 (w), 821 (m), 778 (m), 756 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, s, =C*H*N), 7.28 (2H, d, *J* 8.7 Hz, *o*-Ar), 6.85 (2H, d, *J* 8.7 Hz, *m*-Ar), 6.00 (1H, dt, *J* 15.8, 4.5 Hz, CH_2CH=CH), 5.90 (1H, d, *J* 15.8 Hz, CH_2CH=C*H*), 4.73 (2H, s, =CCH_2OH), 4.45 (1H, d, *J* 10.6 Hz, CH_aH_bAr), 4.38 (1H, d, *J* 10.6 Hz, CH_aH_bAr), 4.34 (2H, t, *J* 7.0 Hz, CH_2N), 4.20–4.16 (4H, m, CH_2CH=CH, OCH_2CH_2), 3.78 (3H, s, O*Me*), 3.30 (2H, br s, 2×O*H*), 1.98 (2H, tt, *J* 7.3, 7.3 Hz, CH_2CH_2N), 1.71–1.62 (2H, m, OCH_2CH_2), 1.59 (3H, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 159.1, 147.9, 131.9, 130.5, 130.5, 129.2 (2C), 122.2, 113.8 (2C), 80.0, 66.6, 64.3, 62.3, 56.1, 55.4, 49.8, 27.0, 25.5, 22.9. Anal. Calcd for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 59.71; H, 7.19; N, 9.94.

4.4. Representative procedure for the preparation of macrocyclic sulfites (21, 23, 25, 27)

*4.4.1. Sulfite (**21**).* The diol **14** (107 mg, 0.26 mmol) was dissolved in anhydrous CH_2Cl_2 (21 mL). Anhydrous Et_3N (0.11 mL, 0.77 mmol)

and DMAP (6 mg, 0.05 mmol) were added. A solution of $SOCl_2$ in anhydrous CH_2Cl_2 (0.36 M, 1 mL, 0.36 mmol) was added over 10 min at 20 °C, under vigorous stirring. After stirring for 1 h, the reaction mixture was concentrated in vacuo. The residue was redissolved in EtOAc, filtered through Celite, and concentrated in vacuo. Purification by flash column chromatography (MeOH/CH_2Cl_2 1:99) gave the sulfite **21** (60 mg, 51%) as white crystals. R_f 0.60 (MeOH/EtOAc 1:99); mp 91–93 °C; dr: 2:1, de: 33% (NMR); IR (neat) ν 3133 (w), 2963 (m), 2933 (m), 2879 (m), 2841 (m), 1716 (s), 1657 (m), 1613 (m), 1587 (w), 1515 (m), 1457 (m), 1390 (m), 1361 (w), 1317 (m), 1304 (m), 1286 (m), 1247 (m), 1194 (m), 1168 (s), 1111 (m), 1028 (s), 1001 (m), 939 (m), 899 (m), 828 (m), 777 (m), 729 (m), 706 (m), 690 (m), 669 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (maj, s, =C*H*N), 7.56 (min, s, =C*H*N), 7.24 (min, d, *J* 8.6 Hz, *o*-Ar), 7.21 (maj, d, *J* 8.6 Hz, *o*-Ar), 6.87 (min, d, *J* 8.7 Hz, *m*-Ar), 6.86 (maj, d, *J* 8.7 Hz, *m*-Ar), 6.82 (both, d, *J* 16.1 Hz, COCH=C*H*), 6.05 (min, d, *J* 16.1 Hz, COC*H*=CH), 6.03 (maj, d, *J* 16.1 Hz, COC*H*=CH), 5.55 (maj, d, *J* 13.3 Hz, =CCH_aH$_b$OSO), 5.49 (min, d, *J* 13.0 Hz, =CCH_aH$_b$OSO), 4.96 (min, d, *J* 13.0 Hz, =CCH$_a$*H*$_b$OSO), 4.95 (maj, d, *J* 13.3 Hz, =CCH$_a$*H*$_b$OSO), 4.48–4.33 (m, CH_2Ar, CH_2N), 4.30–4.24 (m, OCH_aH$_b$CH$_2$), 4.19–4.11 (m, OCH$_a$*H*$_b$CH$_2$), 4.14 (min, d, *J* 10.1 Hz, C(OPMB)CH_aH$_b$OSO), 4.13 (maj, *J* 11.0 Hz, C(OPMB)CH_aH$_b$OSO), 3.92 (maj, d, *J* 11.0 Hz, C(OPMB)CH$_a$*H*$_b$OSO), 3.87 (min, d, *J* 10.1 Hz, C(OPMB)CH$_a$*H*$_b$OSO), 3.79 (both, s, O*Me*), 2.09–2.02 (m, NCH$_2$CH_2), 1.76–1.66 (m, CH_2CH$_2$O), 1.45 (min, s, *Me*), 1.43 (maj, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6 (min), 165.5 (maj), 159.3 (min), 159.2 (maj), 149.2 (min), 148.6 (maj), 143.8 (maj), 143.4 (min), 130.2 (maj), 130.2 (min), 129.1 (2C, min), 128.9 (2C, maj), 123.0 (min), 122.9 (maj), 122.8 (maj), 122.5 (min), 114.0 (2C, min), 113.9 (2C, maj), 76.3 (maj), 76.2 (min), 69.3 (maj), 67.7 (min), 65.3 (maj), 65.2 (min), 63.5 (both), 56.6 (min), 56.0 (maj), 55.4 (both), 49.5 (both), 26.8 (both), 25.0 (min), 24.9 (maj), 20.2 (min), 19.6 (maj); HRMS (ESI): *m*/*z* calcd for $C_{21}H_{27}N_3O_7S$ $[M+H]^+$ 466.1643, found 466.1637.

*4.4.2. Sulfite (**23**).* White crystals, 43% yield; R_f 0.60 (MeOH/EtOAc 1:99); mp 130–131 °C; dr: 3:2, de: 20% (NMR); IR(neat) ν 3133 (w), 3075 (w), 3034 (w), 2963 (m), 2875 (m), 2841 (w), 1714 (s), 1643 (w), 1612 (m), 1585 (w), 1514 (m), 1462 (m), 1446 (m), 1384 (m), 1304 (m), 1250 (s), 1225 (m), 1203 (m), 1174 (m), 1141 (m), 1115 (m), 1056 (m), 1031 (m), 1001 (m), 977 (m), 897 (m), 884 (m), 854 (m), 824, 806, 773, 733, 711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (both, s, =C*H*N), 7.22 (both, d, *J* 8.6 Hz, *o*-Ar), 6.87 (both, d, *J* 8.6 Hz, *m*-Ar), 6.85 (both, d, *J* 16.1 Hz, COCH=C*H*), 6.04 (min, d, *J* 16.1 Hz, COC*H*=CH), 6.03 (maj, d, *J* 16.1 Hz, COC*H*=CH), 5.39–5.38 (m, CH_2OCO), 4.53–4.37 (m, NCH_2), 4.40 (both, d, *J* 10.6 Hz, CH_aH$_b$Ar), 4.34 (both, d, *J* 10.6 Hz, CH$_a$*H*$_b$Ar), 3.94 (min, d, *J* 10.3 Hz, C(OPMB)CH_aH$_b$OSO), 3.91 (maj, d, *J* 9.6 Hz, C(OPMB)CH_aH$_b$OSO), 3.79 (both, s, O*Me*), 3.78 (min, d, *J* 10.3 Hz, C(OPMB)CH$_a$*H*$_b$OSO), 3.74 (maj, d, *J* 9.6 Hz, C(OPMB)CH$_a$*H*$_b$OSO), 3.65–3.48 (m, OCH_2CH$_2$), 1.97–1.86 (m, NCH$_2$CH_2), 1.54–1.46 (m, OCH$_2$CH_2), 1.44 (both, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0 (maj), 165.9 (min), 159.3 (maj), 159.3 (min), 150.3 (maj), 150.0 (min), 144.2 (both), 130.2 (min), 130.2 (maj), 129.1 (2C, maj), 129.0 (2C, min), 123.9 (maj), 123.8 (min), 122.8 (maj), 122.7 (min), 114.0 (2C, maj), 114.0 (2C, min), 76.4 (min), 76.3 (maj), 68.3 (min), 67.4 (maj), 65.3 (maj), 65.2 (min), 62.7 (maj), 62.1 (min), 57.7 (both), 55.4 (both), 50.1 (both), 27.1 (min), 27.0 (maj), 26.3 (min), 26.3 (maj), 19.6 (maj), 19.4 (min); HRMS (ESI): *m*/*z* calcd for $C_{21}H_{27}N_3O_7S$ $[M+H]^+$ 466.1643, found 466.1639.

*4.4.3. Sulfite (**25**).* White crystals, 79% yield; R_f 0.60 (MeOH/EtOAc 1:99); mp 130–131 °C; dr: 1:1 (NMR); IR (neat) ν 3127 (w), 3071 (w), 3044 (w), 3001 (w), 2954 (m), 2930 (m), 2877 (w), 2858 (w), 2836 (w), 1730 (s), 1680 (w), 1613 (m), 1586 (w), 1512 (m), 1454 (m), 1390 (m), 1331 (w), 1303 (m), 1274 (w), 1246 (m), 1233 (m), 1199 (m), 1172 (m), 1133 (m), 1106 (m), 1053 (m), 1036 (m), 1011 (m), 994 (m), 971 (m), 951 (m), 919 (m), 898 (m), 820 (m), 780 (m), 754 (m), 732 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (both, s, =C*H*N), 7.33 (both, d, *J* 8.7 Hz, *o*-Ar), 6.88 (both, d, *J* 8.7 Hz, *m*-Ar), 5.76–5.73 (m, C*H*=C*H*), 5.49 (one, d, *J* 12.5 Hz, CH_aH$_b$OCO), 5.46 (one, d, *J* 12.5 Hz, CH_aH$_b$OCO), 5.32 (one, d, *J* 12.5 Hz, CH$_a$*H*$_b$OCO), 5.30 (one, d, *J* 12.5 Hz, CH$_a$*H*$_b$OCO), 4.54–4.31 (m, CH_2Ar, NCH_2, =CHCH_aH$_b$), 4.28–4.26 (m, =CHCH$_a$*H*$_b$), 4.12–4.02 (m, OCH_aH$_b$CH$_2$), 3.80 (both, s, O*Me*), 3.77–3.67 (m, OCH$_a$*H*$_b$CH$_2$), 2.04–1.92 (m, NCH$_2$CH_2), 1.63 (one, s, *Me*), 1.63 (one, s, *Me*), 1.59–1.47 (m, OCH$_2$CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (both), 159.3 (both), 143.0 (both), 134.9 (one), 134.4 (one), 130.3 (one), 130.3 (one), 129.4 (2C, both), 125.8 (one), 125.6 (one), 124.3 (one), 124.2 (one), 113.9 (2C, both), 80.0 (one), 79.9 (one), 67.0 (both), 62.3 (one), 62.1 (one), 62.0 (one), 61.7 (one), 58.2 (both), 55.4 (both), 50.0 (both), 27.0 (one), 27.0 (one), 26.4 (one), 26.4 (one), 22.2 (one), 22.1 (one). Anal. Calcd for $C_{21}H_{27}N_3O_7S$: C, 54.18; H, 5.85; N, 9.03. Found: C, 54.28; H, 5.77; N, 8.95.

*4.4.4. Sulfite (**27**).* White crystals, 74% yield; R_f 0.60 (MeOH/EtOAc 1:99); mp 92 °C; dr: 1:1 (NMR); IR(neat) ν 3145 (w), 3046 (w), 2994 (m), 2960 (m), 2941 (m), 2922 (m), 2877 (m), 2837 (m), 1735 (s), 1614 (m), 1587 (w), 1512 (m), 1458 (m), 1440 (m), 1387 (m), 1303 (m), 1243 (m), 1201 (m), 1189 (m), 1172 (m), 1145 (m), 1107 (s), 1038 (m), 1006 (m), 981 (m), 941 (m), 924 (m), 904 (s), 839 (m), 813 (m), 804 (m), 786 (m), 757 (m), 739 (m), 717 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (one, s, =C*H*N), 7.64 (one, s, =C*H*N), 7.28 (one, d, *J* 8.6 Hz, *o*-Ar), 7.27 (one, d, *J* 8.6 Hz, *o*-Ar), 6.86 (both, d, *J* 8.6 Hz, *m*-Ar), 5.86–5.84 (m, C*H*=C*H*), 5.60 (one, d, *J* 13.4 Hz, =CCH_aH$_b$OSO), 5.55 (one, d, *J* 13.4 Hz, =CCH_aH$_b$OSO), 4.96 (one, d, *J* 13.4 Hz, =CCH$_a$*H*$_b$OSO), 4.93 (one, d, *J* 13.4 Hz, =CCH$_a$*H*$_b$OSO), 4.51–4.22 (m, CH_2Ar, NCH_2, =CHCH_2, CH$_2$CH_2O), 3.79 (both, s, O*Me*), 1.99–1.84 (m, NCH$_2$CH_2), 1.76–1.64 (m, CH_2CH$_2$O), 1.59 (one, s, *Me*), 1.58 (one, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (both), 159.3 (both), 143.4 (one), 143.3 (one), 134.7 (one), 134.7 (one), 130.2 (one), 130.2 (one), 129.3 (2C, both), 125.4 (one), 125.3 (one), 124.1 (one), 124.1 (one), 113.9 (2C, both), 79.9 (one), 79.9 (one), 66.8 (both), 64.1 (one), 64.1 (one), 62.7 (one), 62.6 (one), 55.4 (both), 55.3 (one), 55.1 (one), 49.5 (both), 27.5 (one), 27.5 (one), 25.5 (both), 22.3 (both); HRMS (ESI): *m*/*z* calcd for $C_{21}H_{27}N_3O_7S$ $[M+H]^+$ 466.1643, found 466.1633.

4.5. Representative procedure for the preparation of deprotected sulfites (22a, 22b, 24, 26, 28)

*4.5.1. Sulfite (**22a**).* The sulfite **21** (259 mg, 0.56 mmol) was dissolved in CH_2Cl_2 (52.8 mL) and water (2.9 mL). DDQ (152 mg, 0.67 mmol) was added, and the mixture was stirred at 20 °C for 6 h. Then the mixture was diluted with EtOAc (260 mL) and washed with 40% aq $NaHSO_3$ (260 mL) and water (2×260 mL). The aqueous phase was extracted with EtOAc (260 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified twice by flash column chromatography (EtOAc/toluene 1:1) to give the deprotected sulfite **22a** (58 mg, 30%, one diastereomer) as white crystals and the sulfite **22b** (one diastereomer). Compound **22a**: R_f 0.42 (MeOH/EtOAc 1:99); mp 121–123 °C; IR(neat) ν 3362 (m), 3134 (m), 2961 (m), 2929 (m), 2876 (m), 1716 (s), 1658 (m), 1467 (m), 1455 (m), 1408 (w), 1392 (w), 1378 (w), 1362 (w), 1304 (m), 1284 (m), 1248 (m), 1194 (m), 1177 (m), 1133 (m), 1105 (m), 1059 (m), 1049 (m), 1033 (m), 1004 (m), 989 (m), 947 (m), 886 (m), 815 (m), 766 (m), 731 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (1H, s, =C*H*N), 6.78 (1H, d, *J* 15.8 Hz, COCH=C*H*), 6.05 (1H, d, *J* 15.8 Hz, COC*H*=CH), 5.66 (1H, d, *J* 13.2 Hz, =CCH_aH$_b$OSO), 4.87 (1H, d, *J* 13.2 Hz, =CCH$_a$*H*$_b$OSO), 4.50 (1H, ddd, *J* 13.9, 7.0, 5.1 Hz, CH_aH$_b$N), 4.38 (1H, ddd, *J* 13.9, 7.0, 5.1 Hz, CH$_a$*H*$_b$N), 4.22 (2H, t, *J* 5.5 Hz, CH$_2$CH_2O), 4.03 (1H, d, *J* 10.3 Hz, C(OH)CH_aH$_b$OSO), 3.86 (1H, d, *J* 10.3 Hz, C(OH)CH$_a$*H*$_b$OSO), 2.99 (1H, br s, O*H*), 2.17–2.01 (2H, m, NCH$_2$CH_2), 1.77–1.65 (2H, m, CH_2CH$_2$O),

1.33 (3H, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 150.8, 143.1, 123.8, 120.9, 71.9, 71.3, 63.3, 55.3, 49.7, 26.6, 25.2, 23.7; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{19}N_3O_6S$ $[M+H]^+$ 346.1067, found 346.1048. Anal. Calcd for $C_{13}H_{19}N_3O_6S$: C, 45.21; H, 5.55; N, 12.17. Found: C, 45.30; H, 5.51; N, 12.08. Compound **22b**: R_f 0.12 (MeOH/EtOAc 1:99); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (1H, s, =C*H*N), 6.81 (1H, d, *J* 15.5 Hz, COCH=C*H*), 6.04 (1H, d, *J* 15.5 Hz, COC*H*=CH), 4.81 (2H, s, =CCH_2OH), 4.56 (1H, d, *J* 8.9 Hz, CH_aH$_b$OSO), 4.42 (1H, d, *J* 8.9 Hz, CH$_a$$H_b$OSO), 4.43–4.39 (2H, m, CH_2N), 4.18 (2H, t, *J* 6.3 Hz, OCH_2CH$_2$), 2.05–1.97 (2H, m, CH_2CH$_2$N), 1.78 (3H, s, *Me*), 1.74–1.67 (2H, m, OCH$_2$CH_2); HRMS (ESI): *m*/*z* calcd for $C_{13}H_{19}N_3O_6S$ $[M+H]^+$ 346.1067, found 346.1094.

*4.5.2. Sulfite (**24**).* White crystals, 47% yield; R_f 0.42 (MeOH/EtOAc 1:99); mp 115–118 °C; dr: 3:2, de: 20% (NMR); IR(neat) ν 3152 (w), 3065 (w), 2965 (m), 2944 (m), 2917 (w), 2872 (w), 2842 (w), 1747 (m), 1725 (m), 1711 (s), 1657 (m), 1611 (w), 1514 (m), 1466 (w), 1449 (m), 1413 (w), 1382 (m), 1324 (m), 1300 (m), 1283 (m), 1264 (m), 1249 (m), 1220 (m), 1179 (m), 1149 (m), 1134 (m), 1027 (m), 1003 (m), 975 (m), 928 (m), 892 (m), 846 (w), 821 (m), 802 (w), 787 (m), 757 (m), 741 (m), 700 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (maj, s, =C*H*N), 7.63 (min, s, =C*H*N), 6.84 (maj, d, *J* 15.6 Hz, COCH=C*H*), 6.82 (min, d, *J* 15.6 Hz, COCH=C*H*), 6.07 (both, d, *J* 15.6 Hz, COC*H*=CH), 5.46 (maj, d, *J* 12.2 Hz, CH_aH$_b$OCO), 5.41 (min, d, *J* 12.3 Hz, CH_aH$_b$OCO), 5.32 (min, d, *J* 12.3 Hz, CH$_a$$H_b$OCO), 5.27 (maj, d, *J* 12.2 Hz, CH$_a$$H_b$OCO), 4.52–4.37 (m, NC$H_2$), 3.91 (min, d, *J* 10.1 Hz, C(OH)CH_aH$_b$OSO), 3.87 (maj, d, *J* 10.0 Hz, C(OH)CH_aH$_b$OSO), 3.77 (maj, d, *J* 10.0 Hz, C(OH)CH$_a$$H_b$OSO), 3.72 (min, d, *J* 10.1 Hz, C(OH)CH$_a$$H_b$OSO), 3.68 (min, dt, *J* 7.2, 7.2 Hz, OCH_aH$_b$CH$_2$), 3.64 (maj, dt, *J* 7.1, 7.1 Hz, OCH_aH$_b$CH$_2$), 3.51 (maj, dt, *J* 7.6, 7.6 Hz, OCH$_a$$H_bCH_2$), 3.47 (min, dt, *J* 7.6, 7.6 Hz, OCH$_a$$H_bCH_2$), 2.69 (both, br s, O*H*), 2.02–1.78 (m, NCH$_2$CH_2), 1.52–1.41 (m, OCH$_2$CH_2), 1.33 (min, s, *Me*), 1.32 (maj, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2 (maj), 166.2 (min), 151.8 (maj), 151.8 (min), 144.3 (maj), 144.2 (min), 123.9 (min), 123.8 (maj), 120.8 (both), 72.2 (min), 72.1 (maj), 70.7 (maj), 69.0 (min), 62.6 (min), 62.0 (maj), 57.5 (min), 57.5 (maj), 50.1 (maj), 50.1 (minor), 27.1 (both), 26.2 (both), 23.6 (both); HRMS (ESI): *m*/*z* calcd for $C_{13}H_{19}N_3O_6S$ $[M+H]^+$ 346.1067, found 346.1068. Anal. Calcd for $C_{13}H_{19}N_3O_6S$: C, 45.21; H, 5.55; N, 12.17. Found: C, 45.06; H, 5.48; N, 12.07.

*4.5.3. Sulfite (**26**).* White crystals, 65% yield; R_f 0.36 (MeOH/EtOAc 1:99); mp 129–130 °C; dr: 1:1 (NMR); IR (neat) ν 3503 (br), 3142 (w), 2970 (m), 2941 (m), 2889 (w), 2871 (w), 1713 (s), 1470 (w), 1447 (m), 1364 (m), 1342 (w), 1264 (m), 1228 (m), 1197 (s) 1150 (m), 1135 (m), 1069 (m), 1053 (m), 983 (m), 970 (m), 946 (m), 920 (m), 871 (m), 839 (w), 821 (w), 805 (w), 777 (m), 731 (m), 678 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (both, s, =C*H*N), 5.88–5.82 (one, m, C*H*=CH), 5.81 (one, d, *J* 15.4 Hz, C*H*=CHCH$_2$), 5.75 (one, d, *J* 15.4 Hz, CH=C*H*CH$_2$), 5.70 (both, d, *J* 12.5 Hz, CH_aH$_b$OCO), 5.16 (one, d, *J* 12.5 Hz, CH$_a$$H_b$OCO), 5.15 (one, d, *J* 12.5 Hz, CH$_a$$H_b$OCO), 4.58–4.42 (m, NC$H_aH_b$, =CHC$H_aH_b$), 4.39–4.23 (m, NCH$_a$$H_b$, =CHCH$_a$$H_b$), 4.07–4.01 (m, OC$H_aH_bCH_2$), 3.74–3.65 (m, OCH$_a$$H_bCH_2$), 3.28 (both, br s, O*H*), 2.07–1.97 (m, NCH$_2$$H_aH_b$), 1.96–1.85 (m, NCH$_2H_a$$H_b$), 1.66–1.54 (m, OCH$_2CH_2$), 1.53 (both, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9 (one), 174.8 (one), 142.7 (one), 142.7 (one), 136.3 (one), 135.2 (one), 124.1 (both), 124.1 (one), 123.9 (one), 74.3 (both), 62.2 (one), 62.0 (one), 61.9 (one), 61.8 (one), 58.9 (one), 58.8 (one), 50.0 (one), 50.0 (one), 26.9 (one), 26.9 (one), 26.4 (one), 26.3 (one), 25.2 (both); HRMS (ESI): *m*/*z* calcd for $C_{13}H_{19}N_3O_6S$ $[M+H]^+$ 346.1067, found 346.1073. Anal. Calcd for $C_{13}H_{19}N_3O_6S$: C, 45.21; H, 5.55; N, 12.17. Found: C, 44.59; H, 5.78; N, 12.07.

*4.5.4. Sulfite (**28**).* White crystals, 67% yield; R_f 0.36 (MeOH/EtOAc 1:99); mp 93–95 °C; dr: 1:1 (NMR); IR (neat) ν 3500 (m), 3151 (w), 2966 (m), 2872 (w), 1719 (s), 1676 (w), 1454 (m), 1443 (m), 1373 (m) 1278 (m), 1198 (m), 1171 (s), 1134 (m), 1075 (w), 1049 (m), 1027 (m), 978 (m), 940 (m), 925 (m), 889 (m), 854 (m), 835 (m), 788 (m), 767 (m), 736 (m), 710 (m), 670 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (one, s, =C*H*N), 7.61 (one, s, =C*H*N), 5.94–5.74 (m, C*H*=C*H*), 5.63 (one, dd, *J* 13.6, 0.4 Hz, =CCH_aH$_b$OSO), 5.54 (one, dd, *J* 13.6, 0.4 Hz, =CCH_aH$_b$OSO), 4.97 (one, dd, *J* 13.6, 0.4 Hz, =CCH$_a$$H_b$OSO), 4.91 (one, dd, *J* 13.6, 0.4 Hz, =CCH$_a$$H_b$OSO), 4.61–4.18 (m, CH$_2CH_aH_b$O, =CHC$H_2$, C$H_2$N), 4.05–3.98 (m, CH$_2CH_a$$H_b$O), 3.36 (both, br s, O*H*), 1.99–1.62 (m, CH_2CH$_2$N, CH_2CH$_2$O), 1.46 (one, s, *Me*), 1.45 (one, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1 (one), 175.0 (one), 143.7 (one), 143.7 (one), 135.4 (one), 135.3 (one), 124.1 (one), 124.0 (one), 123.8 (one), 123.6 (one), 74.1 (one), 74.1 (one), 64.6 (one), 64.6 (one), 63.0 (one), 62.2 (one), 55.7 (one), 54.6 (one), 49.5 (one), 49.5 (one), 27.4 (one), 27.3 (one), 26.0 (one), 25.9 (one), 25.8 (one), 25.8 (one); HRMS (ESI): *m*/*z* calcd for $C_{13}H_{19}N_3O_6S$ $[M+H]^+$ 346.1067, found 346,1063. Anal. Calcd for $C_{13}H_{19}N_3O_6S$: C, 45.21; H, 5.55; N, 12.17. Found: C, 45.56; H, 5.76; N, 11.85.

4.6. Representative procedure for the preparation of macrocyclic malonates (29, 31)

*4.6.1. Malonate (**29**).* The diol **14** (55 mg, 0.13 mmol) was dissolved in anhydrous CH_2Cl_2 (9.74 mL) and anhydrous Et_3N (0.05 mL, 0.36 mmol) and DMAP (3 mg, 0.03 mmol) were added. A solution of malonyl chloride in anhydrous CH_2Cl_2 (0.18 M, 1 mL, 0.18 mmol) was added over 10 min at 20 °C, under vigorous stirring. After stirring for 1½ hours, the reaction mixture was concentrated in vacuo. The residue was redissolved in EtOAc, filtered through Celite, and concentrated in vacuo. Purification by flash column chromatography (MeOH/CH_2Cl_2 1:99) gave the malonate **29** (23 mg, 37%) as a colorless oil. R_f 0.54 (MeOH/EtOAc 1:99); IR (neat) ν 3146 (w), 2956 (m), 2872 (w), 2838 (w), 1751 (s), 1733 (s), 1715 (s), 1656 (w), 1613 (m), 1586 (w), 1514 (m), 1463 (m), 1443 (m), 1409 (w), 1385 (m), 1364 (m), 1300 (m), 1247 (s), 1172 (m), 1146 (m), 1130 (m), 1030 (m), 993 (m), 911 (m), 822 (m), 727 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (1H, s, =C*H*N), 7.24 (2H, d, *J* 8.7 Hz, *o*-Ar), 6.91 (1H, d, *J* 16.0 Hz, COCH=C*H*), 6.87 (2H, d, *J* 8.7 Hz, *m*-Ar), 6.04 (1H, d, *J* 16.0 Hz, COC*H*=CH), 5.36 (1H, d, *J* 12.7 Hz, OCH_aH$_b$C=), 5.21 (1H, d, *J* 12.7 Hz, OCH$_a$$H_b$C=), 4.46 (2H, t, *J* 6.4 Hz, NCH_2), 4.42 (1H, d, *J* 10.5 Hz, CH_aH$_b$Ar), 4.36 (1H, d, *J* 10.5 Hz, CH$_a$$H_b$Ar), 4.29 (1H, d, *J* 11.1 Hz, C(OPMB)CH_aH$_b$O), 4.22 (1H, d, *J* 11.1 Hz, C(OPMB)CH$_a$$H_b$O), 4.28–4.13 (2H, m, CH$_2CH_2$O), 3.80 (3H, s, O*Me*), 3.48 (1H, d, *J* 16.3 Hz, COCH_aH$_b$CO), 3.42 (1H, d, *J* 16.3 Hz, COCH$_a$$H_b$CO), 2.05–1.89 (2H, m, C$H_2CH_2$N), 1.67–1.59 (2H, m, OCH$_2$CH_2), 1.45 (3H, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 165.9, 165.9, 159.3, 149.3, 143.0, 130.3, 129.0 (2C), 124.0, 122.4, 114.0 (2C), 76.1, 69.5, 65.2, 63.0, 59.1, 55.4, 49.5, 41.2, 27.0, 25.5, 20.6; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{29}N_3O_8$ $[M+H]^+$ 488.2033, found 488.2036.

*4.6.2. Malonate (**31**).* White crystals, 34% yield; mp 113–115 °C; R_f 0.54 (MeOH/EtOAc 1:99); IR(neat) ν 3153 (w), 3064 (w), 3039 (w), 2998 (w), 2944 (m), 2916 (w), 2872 (m), 2842 (w), 1747 (s), 1726 (s), 1712 (s), 1657 (m), 1611 (m), 1587 (w), 1514 (m), 1465 (w), 1449 (m), 1413 (w), 1383 (m), 1324 (m), 1300 (m), 1283 (m), 1265 (m), 1249 (m), 1220 (m), 1179 (s), 1149 (m), 1135 (m), 1122 (m), 1059 (m), 1027 (s) 976 (m), 928 (m), 847 (m), 821 (m), 803 (m), 788 (m), 757 (m), 742 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (1H, s, =C*H*N), 7.24 (2H, d, *J* 8.5 Hz, *o*-Ar), 6.94 (1H, d, *J* 16.0 Hz, COCH=C*H*), 6.87 (2H, d, *J* 8.5 Hz, *m*-Ar), 6.08 (1H, d, *J* 16.0 Hz, COC*H*=CH), 5.38 (1H, d, *J* 12.8 Hz, OCH_aH$_b$C=), 5.35 (1H, d, *J* 12.8 Hz, OCH$_a$$H_b$C=), 4.48–4.43 (2H, m, NCH_2), 4.42 (1H, d, *J* 10.7 Hz, CH_aH$_b$Ar), 4.37 (1H, d, *J* 10.7 Hz, CH$_a$$H_b$Ar), 4.27 (1H, d, *J* 11.2 Hz, C(OPMB)CH_aH$_b$O), 4.15 (1H, d, *J* 11.2 Hz, C(OPMB)CH$_a$$H_b$O), 4.00–3.90 (2H, m, CH$_2CH_2$O), 3.80 (3H, s, O*Me*), 3.34 (1H, d, *J* 15.9 Hz, COCH_aH$_b$CO), 3.30 (1H, d, *J* 15.9 Hz, COCH$_a$$H_b$CO), 1.96–1.91 (2H, m, NCH$_2$CH_2), 1.54–1.47 (2H, m, CH_2CH$_2$O), 1.44 (3H, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 166.1,

165.7, 159.3, 149.4, 148.6, 130.3, 129.0 (2C), 124.2, 122.5, 113.9 (2C), 76.3, 69.5, 65.2, 64.2, 58.1, 55.4, 49.6, 41.3, 26.1, 25.3, 20.2; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{29}N_3O_8$ $[M+H]^+$ 488.2033, found 488.2030.

4.7. Representative procedure for the preparation of deprotected macrocyclic malonates (30, 32)

*4.7.1. Malonate (**30**).* The malonate **29** (100 mg, 0.21 mmol) was dissolved in CH_2Cl_2 (19.5 mL) and water (1.1 mL). DDQ (56 mg, 0.25 mmol) was added, and the mixture was stirred at 20 °C for 5½ h. Then the mixture was diluted with EtOAc (100 mL) and washed with 40% aq $NaHSO_3$ (120 mL) and water (2×80 mL). The aqueous phase was extracted with EtOAc (120 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified twice by flash column chromatography (EtOAc/toluene 1:1) to give the deprotected malonate **30** (59 mg, 78%) as a colorless oil. R_f 0.38 (MeOH/EtOAc 1:99); IR (neat) ν 3468 (br), 3148 (w), 2958 (m), 1713 (s), 1658 (m), 1444 (m), 1373 (m), 1328 (m), 1264 (s), 1182 (m), 1136 (s), 1046 (m), 1024 (m), 979 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (1H, s, =C*H*N), 6.92 (1H, d, *J* 15.7 Hz, COCH=C*H*), 6.04 (1H, d, *J* 15.7 Hz, COC*H*=CH), 5.44 (1H, d, *J* 12.6 Hz, =CC$H_a$$H_b$O), 5.17 (1H, d, *J* 12.6 Hz, =CCH$_a$$H_b$O), 4.48 (1H, d, *J* 10.9 Hz, C(OH)CH_aH$_b$O), 4.46 (2H, t, *J* 6.4 Hz, NCH_2), 4.42 (1H, m, CH_2CH_aH$_b$O), 4.03 (1H, d, *J* 10.9 Hz, C(OH)CH$_a$$H_b$O), 4.02 (1H, m, CH_2CH$_a$$H_b$O), 3.48 (1H, d, *J* 17.5 Hz, COCH_aH$_b$CO), 3.45 (1H, d, *J* 17.5 Hz, COCH$_a$$H_b$CO), 2.13 (1H, m, NCH$_2CH_aH_b$), 2.04 (1H, m, NCH$_2CH_a$$H_b$), 1.73 (1H, m, C$H_aH_bCH_2$O), 1.57 (1H, m, CH$_a$$H_bCH_2$O), 1.36 (3H, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 166.1, 165.7, 151.5, 142.5, 124.6, 120.2, 72.2, 71.1, 63.2, 59.1, 49.5, 41.1, 26.9, 25.1, 23.6; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{21}N_3O_7$ $[M+H]^+$ 368.1452, found 368.1449. Anal. Calcd for $C_{16}H_{21}N_3O_7$: C, 52.31; H, 5.76; N, 11.44. Found: C, 52.23; H, 5.71; N, 11.40.

*4.7.2. Malonate (**32**).* White crystals, 69% yield; mp 105–106 °C; R_f 0.38 (MeOH/EtOAc 1:99); IR (neat) ν 3308 (br), 3156 (w), 2986 (w), 2968 (m), 2941 (w), 2873 (w), 1727 (s), 1711 (s), 1650 (w), 1462 (w), 1447 (w), 1422 (w), 1376 (w), 1351 (m), 1324 (m), 1295 (m), 1259 (m), 1239 (m), 1224 (m), 1169 (m), 1075 (m), 1065 (m), 1030 (m), 1007 (m), 981 (m), 841 (m), 782 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (1H, s, =C*H*N), 6.96 (1H, d, *J* 15.7 Hz, COCH=C*H*), 6.10 (1H, d, *J* 15.7 Hz, COC*H*=CH), 5.39 (1H, d, *J* 12.6 Hz, =CC$H_a$$H_b$O), 5.33 (1H, d, *J* 12.6 Hz, =CCH$_a$$H_b$O), 4.49–4.40 (2H, m, NC$H_2$), 4.24 (1H, d, *J* 11.2 Hz, C(OH)CH_aH$_b$O), 4.17 (1H, d, *J* 11.2 Hz, C(OH)CH$_a$$H_b$O), 3.92 (2H, t, *J* 7.3 Hz, CH_2CH_2O), 3.35 (1H, d, *J* 16.4 Hz, COCH_aH$_b$CO), 3.32 (1H, d, *J* 16.4 Hz, COCH$_a$$H_b$CO), 1.96–1.90 (2H, m, NCH$_2$CH_2), 1.52–1.45 (2H, m, CH_2CH$_2$O), 1.35 (3H, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 166.1, 165.9, 151.4, 143.8, 124.2, 120.4, 72.3, 71.4, 64.3, 57.8, 49.7, 41.2, 25.9, 25.4, 24.1; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{21}N_3O_7$ $[M+H]^+$ 368.1452, found 368,1450. Anal. Calcd for $C_{16}H_{21}N_3O_7$: C, 52.31; H, 5.76; N, 11.44. Found: C, 52.18; H, 5.74; N, 11.29.

4.8. Representative procedure for the preparation of dialdehydes (33, 35, 39)

*4.8.1. (±)-(E)-4-(4-Formyl-1H-1,2,3-triazol-1-yl)butyl 2-(4-methoxybenzyloxy)-2-methyl-5-oxopent-3-enoate (**39**).* The diol **20** (51 mg, 0.12 mmol) was dissolved in CH_3CN (2.1 mL). IBX[23] (202 mg, 0.72 mmol) was added, and the suspension was heated to 55 °C. After stirring at 55 °C for 3½ h, the suspension was concentrated in vacuo. The residue was redissolved in ether, filtered, and concentrated in vacuo giving the dialdehyde **39** (50 mg, quantitative yield) as a colorless oil. R_f 0.46 (MeOH/CH_2Cl_2 5:95); IR (neat) ν 3133 (w), 2960 (m), 2937 (m), 2872 (m), 2837 (m), 1733 (s), 1688 (s), 1612 (m), 1531 (m), 1513 (s), 1463 (m), 1443 (m), 1384 (m), 1301 (m), 1245 (s), 1174 (m), 1110 (s), 1092 (s), 1028 (s), 979 (m), 822 (m), 782 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.13 (1H, s, =CC*H*O), 9.62 (1H, d, *J* 7.7 Hz, =CHC*H*O), 8.02 (1H, s, =C*H*N), 7.27 (2H, d, *J* 8.5 Hz, *o*-Ar), 6.99 (1H, d, *J* 15.9 Hz, C*H*=CHCHO), 6.87 (2H, d, *J* 8.5 Hz, *m*-Ar), 6.43 (1H, dd, *J* 15.9, 7.7 Hz, CH=C*H*CHO), 4.44 (2H, s, CH_2Ar), 4.43 (2H, t, *J* 7.1 Hz, CH_2N), 4.23 (2H, t, *J* 6.3 Hz, OCH_2CH$_2$), 3.80 (3H, s, O*Me*), 2.07–1.97 (2H, m, CH_2CH$_2$N), 1.77–1.70 (2H, m, OCH$_2$CH_2), 1.67 (3H, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2, 185.1, 171.3, 159.4, 155.1, 147.9, 132.3, 129.6, 129.1 (2C), 125.3, 113.9 (2C), 80.3, 67.4, 64.9, 55.4, 50.2, 26.9, 25.5, 23.6.

*4.8.2. (±)-(E)-(1-(4-Oxobutyl)-1H-1,2,3-triazol-4-yl)methyl 2-(4-methoxybenzyloxy)-2-methyl-5-oxopent-3-enoate (**35**).* Colorless oil, 98% yield; R_f 0.35 (MeOH/CH_2Cl_2 5:95); IR (neat) ν 3143 (w), 2957 (m), 2938 (m), 2837 (m), 2733 (w), 1723 (s), 1688 (s), 1613 (m), 1514 (s), 1461 (m), 1443 (m), 1386 (m), 1302 (m), 1247 (s), 1175 (m), 1106 (s), 1048 (m), 1028 (m), 979 (m), 913 (m), 821 (m), 729 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (1H, s, CH_2C*H*O), 9.58 (1H, d, *J* 7.8 Hz, =CHC*H*O), 7.58 (1H, s, =C*H*N), 7.25 (2H, d, *J* 8.6 Hz, *o*-Ar), 6.99 (1H, d, *J* 15.9 Hz, C*H*=CHCHO), 6.86 (2H, d, *J* 8.6 Hz, *m*-Ar), 6.38 (1H, dd, *J* 15.9, 7.8 Hz, CH=C*H*CHO), 5.37 (1H, d, *J* 13.2 Hz, CH_aH$_b$OCO), 5.32 (1H, d, *J* 13.2 Hz, CH$_a$$H_b$OCO), 4.44–4.37 (4H, m, CH_2Ar, NCH_2), 3.80 (3H, s, O*Me*), 2.52 (2H, t, *J* 6.8 Hz, CH_2CHO), 2.24–2.15 (2H, m, NCH$_2$CH_2), 1.66 (3H, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3, 193.2, 171.3, 159.4, 155.1, 142.3, 132.2, 129.6, 129.4 (2C), 124.1, 113.9 (2C), 80.2, 67.5, 58.9, 55.4, 49.4, 40.2, 23.8, 22.7.

*4.8.3. (±)-(E)-4-(4-Formyl-1H-1,2,3-triazol-1-yl)butyl 4-(4-methoxybenzyloxy)-4-methyl-5-oxopent-2-enoate (**33**).* Colorless oil, quantitative yield; R_f 0.55 (MeOH/EtOAc 1:99); ^1H NMR (300 MHz, $CDCl_3$) δ 10.15 (1H, s, =CC*H*O), 9.51 (1H, s, C(OPMB)C*H*O), 8.11 (1H, s, =C*H*N), 7.29 (2H, d, *J* 8.8 Hz, *o*-Ar), 6.90 (2H, d, *J* 8.8 Hz, *m*-Ar), 6.87 (1H, d, *J* 15.9 Hz, COCH=C*H*), 6.20 (1H, d, *J* 15.9 Hz, COC*H*=CH), 4.51–4.45 (4H, m, CH_2Ar, NCH_2), 4.20 (2H, t, *J* 6.3 Hz, OCH_2CH$_2$), 3.81 (3H, s, O*Me*), 2.11–2.01 (2H, m, CH_2CH$_2$N), 1.77–1.68 (2H, m, OCH$_2$CH_2), 1.52 (3H, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 185.3, 165.6, 159.6, 148.0, 145.0, 129.6, 129.4 (2C), 125.2, 123.7, 114.1 (2C), 83.3, 66.8, 63.6, 55.4, 50.4, 27.0, 25.7, 19.6.

4.9. Representative procedure for the preparation of macrocyclic amines (34, 36, 40)

*4.9.1. Amine (**40**).* The dialdehyde **39** (43 mg, 0.10 mmol) was dissolved in anhydrous CH_2Cl_2 (6.9 mL). The mixture was cooled to 0 °C, and a solution of veratrylamine in anhydrous CH_2Cl_2 (0.11 M, 1 mL, 0.11 mmol) was added. After stirring at 0 °C for 25 min, Na$(OAc)_3BH$ (65 mg, 0.31 mmol) was added. After stirring at 0 °C for further 15 min, powdered 3 Å molecular sieves (40 mg) were added. The suspension was then stirred at 0 °C for 3 h, whereafter it was quenched with ether (10 mL) and then water (20 mL). After filtration, the mixture was transferred to a separatory funnel with ether (40 mL) and CH_2Cl_2 (20 mL). The organic phase was isolated and washed with a mixture of satd aq $NaHCO_3$ (40 mL) and water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2×30 mL) and ether (30 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography (EtOAc/heptane 3:1) gave the azalide **40** (34 mg, 60%) as an amorphous solid. R_f 0.30 (MeOH/CH_2Cl_2 5:95); IR (neat) ν 3134 (w), 3034 (m), 2996 (m), 2934 (m), 2872 (m), 2834 (m), 1730 (s), 1612 (m), 1589 (m), 1512 (s), 1453 (m), 1418 (m), 1367 (m), 1329 (m), 1301 (m), 1244 (s), 1175 (m), 1108 (s), 1025 (s), 980 (m), 943 (m), 893 (m), 853 (m), 810 (m), 764 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, s, =C*H*N), 7.27 (2H, d, *J* 8.8 Hz, *o*-Ar), 6.96 (1H, s, 2-Ar), 6.89 (1H, d, *J* 8.2 Hz, 6-Ar), 6.85 (2H, d, *J* 8.8 Hz, *m*-Ar), 6.79 (1H, d, *J* 8.2 Hz, 5-Ar), 5.77 (1H, d, *J* 15.7 Hz, C*H*=CHCH$_2$), 5.64 (1H, dt, *J* 15.7, 4.9 Hz, CH=C*H*CH$_2$), 4.43 (1H, d, *J* 10.6 Hz, OCH_aH$_b$Ar), 4.41–4.36 (2H, m, CH$_2$CH_2N), 4.31 (1H, d, *J* 10.6 Hz,

OCH_aH_bAr), 4.26–4.11 (2H, m, CH_2CH_2O), 3.86 (3H, s, O*Me*), 3.84 (3H, s, O*Me*), 3.81 (2H, s, $=CCH_2NDMB$), 3.79 (3H, s, O*Me*), 3.74 (1H, d, *J* 13.3 Hz, NCH_aH_bAr), 3.68 (1H, d, *J* 13.3 Hz, NCH_aH_bAr), 3.21 (2H, d, *J* 4.9 Hz, $CH=CHCH_2$), 2.10–2.01 (2H, m, CH_2CH_2N), 1.68–1.62 (2H, m, CH_2CH_2O), 1.53 (3H, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 159.2, 149.0, 148.2, 147.4, 131.7, 131.6, 131.0, 130.7, 129.3 (2C), 122.0, 121.1, 113.8 (2C), 112.1, 110.9, 80.3, 66.7, 63.4, 60.6, 56.1, 56.0, 56.0, 55.4, 50.1, 49.4, 26.6, 26.5, 22.4; HRMS (ESI): *m*/*z* calcd for $C_{30}H_{38}N_4O_6$ $[M+H]^+$ 551.2864, found 551.2859.

*4.9.2. Amine (**36**).* White solid, 46% yield; R_f 0.17 ($MeOH/CH_2Cl_2$ 5:95); mp 141–143 °C; IR(neat) ν 3129 (w), 2994 (w), 2966 (w), 2937 (m), 2915 (w), 2875 (w), 2837 (w), 2797 (m), 1718 (s), 1614 (m), 1589 (w), 1516 (s), 1452 (m), 1420 (w), 1389 (w), 1375 (w), 1328 (w), 1252 (s), 1237 (m), 1184 (m), 1160 (m), 1122 (s), 1058 (w), 1024 (m), 966 (w), 929 (w), 879 (w), 856 (w), 826 (m), 805 (m), 761 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (1H, s, $=CHN$), 7.32 (2H, d, *J* 8.7 Hz, *o*-Ar), 6.87 (2H, d, *J* 8.7 Hz, *m*-Ar), 6.83 (1H, s, 2-Ar), 6.76 (2H, s, 5-Ar, 6-Ar), 5.66 (1H, dt, *J* 15.7, 6.0 Hz, $CH=CHCH_2$), 5.49 (1H, d, *J* 12.1 Hz, CH_aH_bOCO), 5.44 (1H, d, *J* 15.7 Hz, $CH=CHCH_2$), 5.31 (1H, d, *J* 12.1 Hz, CH_aH_bOCO), 4.49 (1H, d, *J* 10.6 Hz, OCH_aH_bAr), 4.41 (1H, d, *J* 10.6 Hz, OCH_aH_bAr), 4.39–4.28 (2H, m, $=NNCH_2$), 3.85 (3H, s, O*Me*), 3.84 (3H, s, O*Me*), 3.80 (3H, s, O*Me*), 3.47 (1H, d, *J* 13.9 Hz, NCH_aH_bAr), 3.42 (1H, d, *J* 13.9 Hz, NCH_aH_bAr), 2.89 (2H, d, *J* 6.0 Hz, $CH=CHCH_2$), 2.15–2.09 (2H, m, CH_2CH_2NDMB), 1.90–1.79 (2H, m, $=NNCH_2CH_2$), 1.58 (3H, s, *Me*), 1.27–1.15 (2H, m, CH_2CH_2NDMB); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 159.2, 149.0, 148.1, 142.9, 132.3, 132.3, 131.9, 130.6, 129.3 (2C), 124.7, 120.9, 113.8 (2C), 111.8, 110.8, 80.4, 66.7, 59.3, 58.0, 56.0, 56.0, 55.4, 54.8, 52.7, 50.1, 27.7, 22.7, 20.9; HRMS (ESI): *m*/*z* calcd for $C_{30}H_{38}N_4O_6$ $[M+H]^+$ 551.2864, found 551.2862.

*4.9.3. Amine (**34**).* Yield (9%); R_f 0.30 (MeOH/EtOAc 1:99); ^1H NMR (500 MHz, CD_3OD) δ 7.57 (1H, s, $=CHN$), 7.18 (2H, d, *J* 8.6 Hz, *o*-Ar), 7.05 (1H, m, 2-Ar), 6.90–6.83 (2H, m, 5-Ar, 6-Ar), 6.78 (2H, d, *J* 8.6 Hz, *m*-Ar), 6.65 (1H, d, *J* 16.1 Hz, $COCH=CH$), 5.85 (1H, d, *J* 16.1 Hz, $COCH=CH$), 4.41 (1H, d, *J* 11.0 Hz, OCH_aH_bAr), 4.35 (1H, m, $CH_2CH_aH_bN$), 4.28 (1H, d, *J* 11.0 Hz, OCH_aH_bAr), 4.27 (1H, m, $CH_2CH_aH_bN$), 4.23 (1H, m, $OCH_aH_bCH_2$), 4.16 (1H, d, *J* 13.6 Hz, NCH_aH_bAr), 4.08 (1H, m, $OCH_aH_bCH_2$), 3.82 (3H, s, O*Me*), 3.74 (6H, s, 2×O*Me*), 3.65 (1H, d, *J* 14.3 Hz, $=CCH_aH_bNDMB$), 3.57 (1H, d, *J* 13.6 Hz, NCH_aH_bAr), 3.43 (1H, d, *J* 14.3 Hz, $=CCH_aH_bNDMB$), 3.05 (1H, d, *J* 14.2 Hz, $C(OPMB)CH_aH_bN$), 2.85 (1H, d, *J* 14.2 Hz, $C(OPMB)CH_aH_bN$), 2.10–1.97 (2H, m, CH_2CH_2N), 1.84–1.74 (2H, m, OCH_2CH_2), 1.35 (3H, s, *Me*); HRMS (ESI): *m*/*z* calcd for $C_{30}H_{38}N_4O_6$ $[M+H]^+$ 551.2864, found 551.2845.

4.10. Representative procedure for the preparation of monodeprotected macrocyclic amines (37, 41)

*4.10.1. Amine (**37**).* The amine **36** (15 mg, 0.027 mmol) was dissolved in CH_2Cl_2 (0.70 mL) and water (0.14 mL). DDQ (18 mg, 0.08 mmol) was added, and the reaction mixture was stirred at 20 °C for 21 h. Subsequently, the mixture was concentrated in vacuo, and the residue was purified by flash column chromatography (EtOAc/toluene 4:1+0.5% Et_3N) to give the monodeprotected amine **37** (8 mg, 69%) as a colorless film. R_f 0.07 ($MeOH/CH_2Cl_2$ 5:95); ^1H NMR (300 MHz, CD_3OD) δ 7.94 (1H, s, $=CHN$), 6.95 (1H, d, *J* 1.6 Hz, 2-Ar), 6.89 (1H, d, *J* 8.2 Hz, 6-Ar), 6.83 (1H, dd, *J* 8.2, 1.6 Hz, 5-Ar), 5.71 (1H, ddd, *J* 15.4, 8.5, 4.4 Hz, $CH=CHCH_2$), 5.60 (1H, d, *J* 12.3 Hz, CH_aH_bOCO), 5.44 (1H, d, *J* 15.4 Hz, $CH=CHCH_2$), 5.11 (1H, d, *J* 12.3 Hz, CH_aH_bOCO), 4.46–4.41 (2H, m, $=NNCH_2$), 3.83 (3H, s, O*Me*), 3.81 (3H, s, O*Me*), 3.58 (1H, d, *J* 13.0 Hz, NCH_aH_bAr), 3.51 (1H, d, *J* 13.0 Hz, NCH_aH_bAr), 3.07 (1H, ddd, *J* 14.7, 4.4, 1.6 Hz, $CH=CHCH_aH_b$), 2.85 (1H, dd, *J* 14.7, 8.5 Hz, $CH=CHCH_aH_b$), 2.15 (2H, t, *J* 8.1 Hz, CH_2CH_2NDMB), 1.90 (1H, m, $=NNCH_2CH_aCH_b$), 1.75 (1H, m, $=NNCH_2CH_aH_b$), 1.43 (3H, s, *Me*), 1.33 (1H, m, $CH_aH_bCH_2NDMB$), 1.07 (1H, m, $CH_aH_bCH_2NDMB$); HRMS (ESI): *m*/*z* calcd for $C_{22}H_{30}N_4O_5$ $[M+H]^+$ 431.2289, found 431.2289.

*4.10.2. Amine (**41**).* 33% yield; R_f 0.10 ($MeOH/CH_2Cl_2$ 5:95); ^1H NMR (500 MHz, CD_3OD) δ 7.87 (1H, s, $=CHN$), 7.07 (1H, s, 2-Ar), 6.94 (1H, d, *J* 8.2 Hz, 6-Ar), 6.91 (1H, d, *J* 8.2 Hz, 5-Ar), 5.65 (1H, d, *J* 15.6 Hz, $CH=CHCH_2$), 5.57 (1H, ddd, *J* 15.6, 6.2, 4.8 Hz, $CH=CHCH_2$), 4.47 (1H, m, $CH_2CH_aH_bN$), 4.39 (1H, m, $CH_2CH_aH_bN$), 4.27 (1H, m, $CH_2CH_aH_bO$), 4.03 (1H, m, $CH_2CH_aH_bO$), 3.85 (3H, s, O*Me*), 3.82 (3H, s, O*Me*), 3.79–3.77 (2H, m, NCH_2Ar), 3.74 (2H, s, $=CCH_2NDMB$), 3.25 (1H, m, $CH=CHCH_aH_b$), 3.18 (1H, dd, *J* 15.5, 6.2 Hz, $CH=CHCH_aH_b$), 2.04 (2H, m, CH_2CH_2N), 1.66 (1H, m, $CH_aH_bCH_2O$), 1.57 (1H, m, $CH_aH_bCH_2O$), 1.36 (3H, s, *Me*); HRMS (ESI): *m*/*z* calcd for $C_{22}H_{30}N_4O_5$ $[M+H]^+$ 431.2289, found 431.2281.

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Supplementary data

Copies of NMR spectra for compounds **1**–**37**, **39**–**41**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.10.071. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. *Nat. Rev. Drug Discovery* **2008**, *7*, 608–624.
2. Wessjohann, L. A.; Ruijter, E.; Garcia-Rivera, D.; Brandt, W. *Mol. Diversity* **2005**, *9*, 171–186.
3. Wessjohann, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 303–309.
4. Nielsen, J. *Curr. Opin. Chem. Biol.* **2002**, *6*, 297–305.
5. Kotha, S.; Singh, K. *Eur. J. Org. Chem.* **2007**, 5909–5916; Cordier, C.; Morton, D.; Leach, S.; Woodhall, T.; O'Leary-Steele, C.; Warriner, S.; Nelson, A. *Org. Biomol. Chem.* **2008**, *6*, 1734–1737; Hurevich, M.; Tal-Gan, Y.; Klein, S.; Barda, Y.; Levitzki, A.; Gilon, C. *J. Pept. Sci.* **2010**, *16*, 178–185; Schmidt, D. R.; Kwon, O.; Schreiber, S. L. *J. Comb. Chem.* **2004**, *6*, 286–292; Cisar, J. S.; Ferreras, J. A.; Soni, R. K.; Quadri, L. E. N.; Tan, D. S. *J. Am. Chem. Soc.* **2007**, *129*, 7752–7753; Rivera, D. G.; Vercillo, O. E.; Wessjohann, L. A. *Org. Biomol. Chem.* **2008**, *6*, 1787–1795; Zacuto, M. J.; Leighton, J. L. *Org. Lett.* **2005**, *7*, 5525–5527; Beeler, A. B.; Acquilano, D. E.; Su, Q.; Yan, F.; Roth, B. L.; Panek, J. S.; Porco, J. A., Jr. *J. Comb. Chem.* **2005**, *7*, 673–681; Kim, Y.-K.; Arai, M. A.; Arai, T.; Lamenzo, J. O.; Dean, E. F., III; Patterson, N.; Clemons, P. A.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 14740–14745.
6. Wingstrand, M. J.; Madsen, C. M.; Clausen, M. H. *Tetrahedron Lett.* **2009**, *50*, 693–695.
7. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064; Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.
8. Jung, M. E.; Duclos, B. A. *Tetrahedron Lett.* **2004**, *45*, 107–109.
9. Calderon, N. *Acc. Chem. Res.* **1972**, *5*, 127–132; Calderon, N.; Chen, H. Y.; Scott, K. W. *Tetrahedron Lett.* **1967**, *34*, 3327–3329.
10. For the *S*-enantiomer of **6**, see: Tanner, D.; Somfai, P. *Tetrahedron* **1987**, *43*, 4395–4406.
11. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
12. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
13. Takaku, H.; Ueda, S.; Ito, T. *Tetrahedron Lett.* **1983**, *24*, 5363–5366; Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139–4142.
14. Rai, A. N.; Basu, A. *Tetrahedron Lett.* **2003**, *44*, 2267–2269.
15. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660.
16. Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888–890.
17. Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522–524.
18. Hartman, C.; Meyer, V. *Chem. Ber.* **1893**, *26*, 1727–1732.
19. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
20. Davies, S. G.; Ichihara, O. *Tetrahedron Lett.* **1998**, *39*, 6045–6048.
21. Tarrade-Matha, A.; Valle, M. S.; Tercinier, P.; Dauban, P.; Dodd, R. H. *Eur. J. Org. Chem.* **2009**, 673–686.
22. Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738–3740.
23. Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.