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Stereoselective synthesis of 2-substituted 3-azabicyclo[3.2.0]heptan-2-ones by [2+2]-cycloaddition of *N*-allyl-β-*N*-keteniminium salts derived from (*R*)-vinylglycinol

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Abstract

A stereoselective synthesis of (1*R*,2*R*,5*S*)-2-benzyloxymethyl-3-azabicyclo[3.2.0]heptan-2-one was achieved, by intramolecular [2+2]-cycloaddition of (*R*)-vinylglycinol-derived *N*-allyl-β-*N*-keteniminium salts, with high facial diastereoselection. The regio- and stereochemical courses have been qualitatively investigated by Molecular Mechanics calculations.

1. Introduction

The diastereoselective synthesis of natural or synthetic substituted pyrrolidines is an important topic in organic synthesis because of their presence as constituents of biologically active compounds. For instance, α-kainic acid[1] and acromelic acids[1] show remarkable neuroexcitatory effects,[2] although with different modes of action.[3] On the other hand, 2,3,4-trisubstituted pyrrolidines are components of cyclic peptides[4] or alkaloids.[5] In particular, 3,4-dihydroxy-2-hydroxymethyl pyrrolidines are inhibitors of several glycosidases.[6] Therefore, chiral 2-substituted-3-azabicyclo[3.2.0]heptan-6-ones are useful intermediates for the synthesis of chiral heterocycles by elaboration of the four-membered ring.

The inter- and intramolecular [2+2]-cycloadditions of keteniminium salts to an olefin were first introduced by Ghosez et al.[7] as an alternative to the [2+2]-cycloaddition of a ketene[8] with olefins. Cyclobutanones,[7a] fused bicyclobutanones[7b] and azabicyclobutanones[7c] were prepared in good

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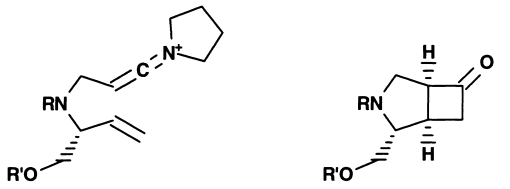
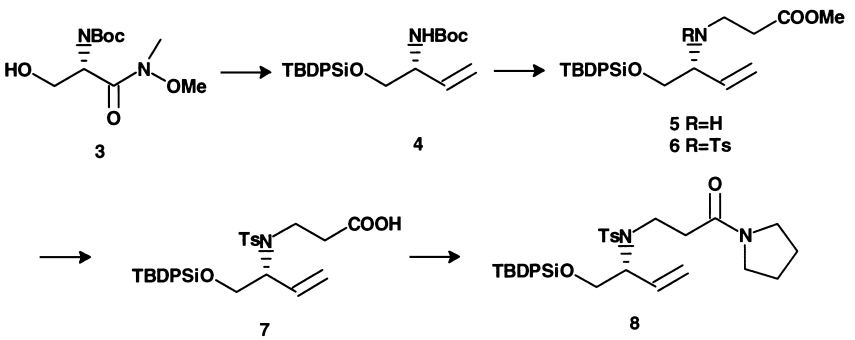
yields by this method. Moreover, high enantioselectivity[9] was observed in the inter- and intramolecular [2+2]-cycloaddition of chiral keteniminium salts. Less attention,[10] however, has been paid to the stereochemical course of this [2+2]-cycloaddition when a stereogenic centre is part of the olefin compound.

Following our studies[11] on the electrophile-mediated functionalization of chiral allyl amines, we focused our interest on the intramolecular asymmetric [2+2]-cycloaddition of *N*-allyl-β-*N*-keteniminium salts **1** derived from (*R*)-vinylglycinol as a way to prepare compounds **2**. This communication deals with our first results.



1 2

For this purpose, compound **8** was prepared (Scheme 1) starting from L-serine, which was converted into the known[12] Weinreb amide **3**. After protection of the hydroxyl group as a silyl ether (*t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2; 89%), the α-amino amide was converted[13] into the allyl amine[14] **4**, by treatment with $LiAlH_4$ (1 M, THF; 0°C), followed by Wittig methylation ($Ph_3P^+CH_3Br^-$/KHMDS, –78°C→rt; 73% from **3**).



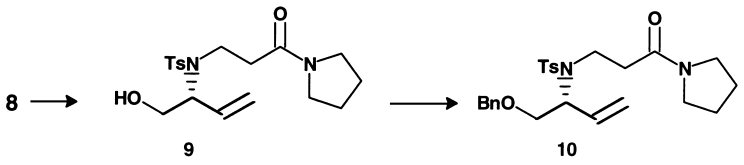
3 4 7 8

Scheme 1.

The Boc-protecting group in **4** was removed (Scheme 1), according to the method of Ohfune et al.,[15] under neutral conditions (TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 20 min; NH_4Cl; 98%) to give the corresponding free amine, which in turn, by a Michael-type reaction with methyl acrylate in MeOH, afforded the α-amino ester[16] **5** in 94% yield. The secondary amine **5** was protected (TsCl, CH_2Cl_2, Et_3N, 0°C→rt; 98%) as *N*-Ts **6**, and the ester function was hydrolyzed (LiOH, acetone/H_2O; 86%). The coupling[17] (BOPCl, DMAP cat., CH_2Cl_2, 80%) of acid **7** with pyrrolidine finally afforded the required amide **8**.

Reaction of compound **8** with triflic anhydride and 2,6-di-*t*-butyl-4-methylpyridine in 1,2-dichloroethane under reflux for 3 h, followed by hydrolysis (H_2O/CCl_4, reflux), gave a complex mixture of products. A cleaner reaction occurred when the cycloaddition reaction was carried out at room temperature with ultrasound activation, but the main product (60% yield) was the alcohol **9**.

To overcome these by-reactions we turned our attention to the use of benzyl ether as a protecting group for the hydroxyl. This switch was performed by treatment of **8** with TBAF (1 M THF; 98% yield), followed by conversion (NaH, BnBr, TBAI, THF; 85%) of the free alcohol **9** into benzyl ether **10** (Scheme 2).

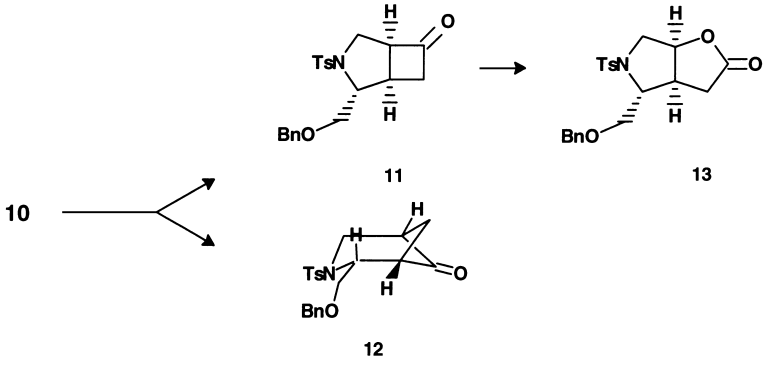


Scheme 2.

The results of the [2+2]-cycloaddition reaction on the allyl amine **10** under different conditions are reported in Table 1. A solution of Tf_2O was added to a solution of substrate **10** and 2,6-di-*t*-butyl-4-methylpyridine at room temperature. The resulting mixture was held under reflux or sonicated. In both cases, compound **10** was converted into a mixture of (1*R*,2*R*,5*S*)-2-benzyloxymethyl-*N*-(4-methylbenzenesulfonyl) 3-azabicyclo[3.2.0]heptan-6-one **11** and the [3.1.1]-isomer **12** (Scheme 3).

Table 1
Results of intramolecular cycloaddition of keteniminium salt derived from protected (*R*)-vinylglycinol **10**

Reaction conditions	Yield (%)	**11**	**12**
1. $ClCH_2CH_2Cl$/reflux, 3 h	35	4	1
2. $ClCH_2CH_2Cl$/ultrasound activation, 24 h	60	11	1
3. CH_2Cl_2/reflux, 24 h	68	10	1



Scheme 3.

As shown in Table 1 the [3.2.0]-isomer **11** (dr = >95/5) was obtained as the major product, when the reaction was run at room temperature under ultrasound activation (entry 2), although similar results were obtained in CH_2Cl_2 under reflux (entry 3).

The two adducts were assigned the structures **11** and **12** on the basis of the ^1H and ^{13}C NMR spectral data (Table 2), as well as COSY and HETCOR experiments. The assignments are in agreement with the values reported in the literature for similar compounds.[18]

Table 2
Selected ^1H- and ^{13}C NMR spectral data for azabicyclo compounds **11** and **12**

Position	**11**		**12**	
	δ_C	δ_H (mult)	δ_C	δ_H (mult)
C-1	32.88	2.99 (ddd)	56.10	2.94 (br q)
C-2	65.19	4.03 (dd)	64.45	4.53 (dd)
C-4	50.18	3.83 (dd) 3.56 (dd)	52.10	4.02 (dd) 3.80 (dd)
C-5	64.28	3.60 (m)	58.99	3.16 (br t)
C-7	51.73	3.07 (ddd) 3.56 (dd)	19.34	3.45 (ddd) 1.69 (dt)
C-6	208.06		208.60	

Coupling constants (Hz): **11**, $J_{1,2} \cong 0$, $J_{1,5} = 7$, $J_{1,7A} = 9$, $J_{1,7B} = 3.5$, $J_{4A,5} = 1$, $J_{4B,5} = 8$, $J_{5,7A} = 4.5$, $J_{5,7B} = 3.5$; **12**, $J_{1.2} = 5$, $J_{1.7A} = 6.5$, $J_{1,7B} = 5.5$, $J_{4A,5} = 5.5$, $J_{4B,5} = 1$, $J_{5,7A} = 7.5$, $J_{5,7B} = 5.5$

Table 2 shows that the signal of the 7-methylene in the ^{13}C NMR in **11** is shifted downfield due to the proximity of the C=O group. By contrast, in compound **12**, the corresponding signal appears to highfield, whereas the resonance of the C-1 methine is now shifted downfield by the carbonyl group. In **11** the value of the $J_{1,5}$ (7 Hz) established a *cis*-relationship between H-1 and H-5 protons,[18] while the small coupling ($J_{1,2} \cong 0$) requires the dihedral angle between H-1 and H-2 to be close to 90°. The assignment of the structure was confirmed by facile ring expansion of **11,** under Baeyer–Villiger[19] conditions, to give the lactone **13**. Notably, the long-range coupling between 7-CH_2 protons and H-5 in **11** (see Table 2) disappeared in the bicyclo compound **13**.

The regio- and stereochemical course of the cycloaddition was qualitatively investigated by Molecular Mechanics calculations. Two possible transition state structures TS1 and TS2 were envisaged. TS1 leads to the stereoisomers with a *syn* relationship between H-1 and H-2, i.e. the products not experimentally observed. On the other hand, TS2 showed the correct geometry of the keteniminium and olefin fragments to give both the regioisomers **11** and **12**.

A conformational search[20] was performed on the keteniminium salt structure **1** (R = Ts, R′ = Bn). The analysis of the data showed that, within 6 kcal/mol from the global minimum,[20] this structure exists only in conformations, such as **C**, leading to TS2 (Fig. 1).

A conformational search[20] was also carried out on the regioisomers **11** and **12** and the relative stability of the two isomers was obtained from the computed energies[21] of their more stable conformers. The results indicated a strong preference (–5.75 kcal/mol) for the [3.2.0]-isomer **11**.

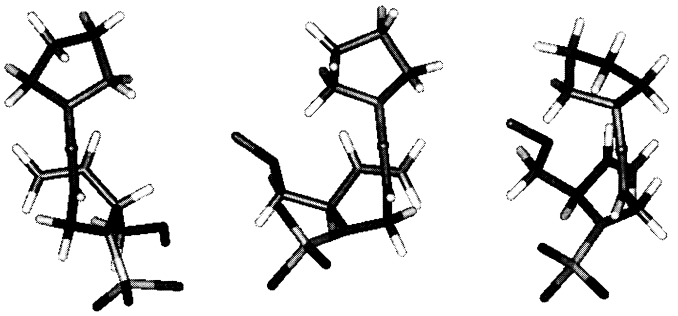


Figure 1. Structure C describes one of the conformations found in the conformational search of **1** (R = Ts, R′ = Bn). Aromatic rings are omitted for the sake of clarity

In conclusion, this communication has shown that intramolecular [2+2]-cycloaddition of an *N*-allyl-β-*N*-keteniminium salt derived from protected (*R*)-vinylglycinol **10**, affords the azabicyclo compounds **11** with high facial diastereoselectivity. Studies on the utilization of compounds **11** and **13** for the synthesis of biologically relevant 2,3,4-trisubstituted pyrrolidines are in progress.

Acknowledgements

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14. Melting points were determined in open capillaries and are uncorrected. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) were run in $CDCl_3$, unless otherwise reported. Coupling constants are given in hertz. The proton and carbon signals of the protecting groups (*t*-BuPh$_2$Si, Ts) are not reported. Optical rotations were determined at 23°C (concentration g/100 ml). Compound **4**: m.p. 41–42°C; $[\alpha]_D = +25.4$ (*c* 1.7, $CHCl_3$); anal. calcd for $C_{25}H_{35}NO_3Si$: C, 70.55; H, 8.29; N, 3.29; found: C, 70.56; H, 8.30; N, 3.28; ^{1}H NMR δ: 5.84 (1H, ddd, $J = 17.0, 10.0, 5.0$, =CH), 5.22 (1H, dt, $J = 17.0, 1.5$, =CH_AH$_B$), 5.16 (1H, dt, $J = 10.0, 1.5$, =CH$_A$$H_B$), 4.24 (1H, m, $\sum J = 25.0$, CHN), 3.74 (1H, dd, $J = 10.0, 4.5$, CH_CH$_D$OSi), 3.64 (1H, dd, $J = 10.0, 4.5$, CH$_C$$H_D$OSi); ^{13}C NMR δ: 155.45 (s, NCO), 136.49 (d, CH=), 115.65 (t, =CH$_2$), 66.06 (t, CH$_2$OSi), 64.30 (d, CHN). Compound **5**: $[\alpha]_D = -2.2$ (*c* 2.0, $CHCl_3$); ^{1}H NMR δ: 5.56 (1H, ddd, $J = 17.0, 10.0, 8.0$, CH=), 5.16 (1H, br d, $J = 17.0$, =CH_AH$_B$), 5.13 (1H, br d, $J = 10.0$, =CH$_A$$H_B$), 3.68 (3H, s, OCH$_3$), 3.62 (1H, dd, $J = 10.0, 5.0$, CH_CH$_D$Si), 3.57 (1H, dd, $J = 10.0, 9.0$, CH$_C$$H_D$Si), 3.22 (1H, td, $J = 8.5$, CHN), 2.91 (1H, dt, $J = 12.0, 6.5$, CH_EH$_F$N), 2.79 (1H, dt, $J = 12.0, 6.5$, CH$_E$$H_F$N), 2.57 (1H, dt, $J = 17.0, 6.5$, CH_GH$_L$CO), 2.49 (1H, $J = 17.0, 6.5$, CH$_G$$H_L$CO); ^{13}C NMR δ: 173.07 (s, COO), 137.22 (d, =CH), 117.97 (t, =CH$_2$), 66.64 (t, CH$_2$OSi), 61.10 (d, CHN), 51.58 (q, OCH$_3$), 42.37 (t, CH$_2$N), 34.43 (t, *C*H$_2$CO). Compound **6**: $[\alpha]_D = -3.4$ (*c* 3.5, $CHCl_3$); anal. calcd for $C_{31}H_{39}NO_5SSi$: C, 65.81; H, 6.95; N, 2.48; found: C, 65.80; H, 6.97; N, 2.49; ^{1}H NMR δ: 5.60 (1H, ddd, $J = 17.0, 10.0, 6.0$, CH=), 5.11 (1H, dt, $J = 10.5, 1.5$, =CH_AH$_B$), 4.98 (1H, dt, $J = 17.0, 1.5$, =CH$_A$$H_B$), 4.48 (1H, qt, $J = 6.0, 1.5$, CHN), 3.74 (1H, dd, $J = 11.0, 6.0$, CH_CH$_D$OSi), 3.70 (1H, dd, $J = 11.0, 7.0$, CH$_C$$H_D$OSi), 3.62 (3H, s, OCH$_3$), 3.51 (1H, ddd, $J = 16.0, 10.0, 6.0$, CH_EH$_F$N), 3.37 (1H, ddd, $J = 16.0, 10.0, 6.0$, CH$_E$$H_F$N), 2.82 (1H, ddd, $J = 16.0, 10.0, 6.0$, CH_GH$_L$CO), 2.71 (1H, ddd, $J = 16.0, 10.0, 6.0$, CH$_G$$H_L$CO); ^{13}C NMR δ: 171.95 (s, COO), 133.24 (d, =CH), 119.11 (t, =CH$_2$), 64.64 (t, CH$_2$OSi), 61.36 (d, CHN), 51.54 (q, OCH$_3$), 40.59 (t, CH$_2$N), 35.70 (t, *C*H$_2$CO). Compound **7**: $[\alpha]_D = -2.4$ (*c* 1.1, $CHCl_3$); ^{1}H NMR δ: 5.60 (1H, br d, $J = 17.0, 10.0, 6.0$, CH=), 5.07 (1H, br d, $J = 17.0$, =CH_AH$_B$), 4.97 (1H, br d, $J = 10.0$, =CH$_A$$H_B$), 4.41 (1H, br q, $J = 6.0$, CHN), 3.70 (2H, d, $J = 6.0$, CH$_2$OSi), 3.49 (1H, dt, $J = 15.0, 7.0$, CH_CH$_D$N), 3.37 (1H, dt, $J = 15.0, 7.0$, CH$_C$$H_D$N), 2.71 (1H, dt, $J = 17.0, 7.0$, CH_EH$_F$CO), 2.64 (1H, dt, $J = 17.0, 7.0$, CH$_E$$H_F$CO); ^{13}C NMR δ: 177.10 (s, *C*OOH), 133.45 (d, CH=), 64.43 (t, CH$_2$OSi), 61.34 (d, CHN), 40.94 (t, CH$_2$N), 36.64 (t, *C*H$_2$CO). Compound **8**: $[\alpha]_D = -9.5$ (*c* 3.0, $CHCl_3$); anal. calcd for $C_{34}H_{44}N_2O_4SSi$: C, 67.51; H, 7.33; N, 4.63; found: C, 67.50; H, 7.35; N, 4.60; ^{1}H NMR δ: 5.56 (1H, ddd, $J = 17.0, 10.0, 6.0$, CH=), 5.08 (1H, dt, $J = 10.5, 1.5$, =CH_AH$_B$), 4.95 (1H,dt, $J = 17.0, 1.5$, =CH$_A$$H_B$), 4.53 (1H, qt, $J = 6.0, 5.0, 1.5$, CHN), 3.75 (1H, dd, $J = 11.0, 6.5$, CH_CH$_D$OSi), 3.71 (1H, dd, $J = 11.0, 6.5$, CH$_C$$H_D$OSi), 3.49 (1H, ddd, $J = 16.0, 10.0, 6.0$, CH$_C$$H_D$OSi), 3.40 (1H, ddd, $J = 16.0, 10.0, 6.0$, CH$_E$$H_FNSO_2$), 3.38 (2H, m, CH$_2$NCO), 3.31 (1H, dt, $J = 10.0, 6.5$, CH_GH$_L$NCO), 3.17 (1H, ddd, $J = 10.0, 7.0, 6.0$, CH$_G$$H_L$NCO), 2.82 (1H, ddd, $J = 16.0, 10.0, 6.0$, CH_MH$_N$NCO), 2.66 (1H, ddd, $J = 16.0, 10.0, 6.0$, CH$_M$$H_N$CO), 1.73–1.94 (4H, m, 2×CH$_2$); ^{13}C NMR δ: 169.53 (s, NCO), 133.15 (d, CH=), 119.09 (t, =CH$_2$), 64.60 (t, CH$_2$OSi), 61.64 (d, CHN), 46.35 (t, *C*H$_2$NCO), 45.40 (t, *C*H$_2$NCO), 41.05 (t, CH$_2$NSO$_2$), 36.55 (t, *C*H$_2$CO), 25.95 (t, CH$_2$), 24.35 (t, CH$_2$). Compound **9**: $[\alpha]_D = -59.5$ (*c* 1.1, $CHCl_3$); anal. calcd for $C_{18}H_{26}N_2O_4SSi$: C, 58.99; H, 7.15; N, 7.64; found: C, 60.04; H, 7.19; N, 7.60; ^{1}H NMR δ: 5.52 (1H, ddd, $J = 17.0, 10.5, 6.0$, CH=), 5.13 (1H, dt, $J = 10.5, 1.5$, =CH_AH$_B$), 5.09 (1H, dt, $J = 17.0, 1.5$, =CH$_A$$H_B$), 4.51 (1H, dddt, $J = 8.0, 6.0, 5.0, 1.5$, CHN), 4.06 (1H, s, OH), 3.82 (1H, br dd, $J = 12.0, 8.0$, CH_CH$_D$OSi), 3.73 (1H, dd, $J = 12.0, 5.0$, CH$_C$$H_D$OSi), 3.49 (1H, ddd, $J = 15.0, 9.0, 6.0$, CH_EH$_F$NTs), 3.41 (1H, ddd, $J = 15.0, 6.5, 5.0$, CH$_E$$H_F$NTs), 3.38 (2H, m, C$H_2$NCO), 3.33 (2H, t, $J = 6.5$, *C*H$_2$NCO), 2.99 (1H, ddd, $J = 16.0, 9.0, 6.5$, CH_GH$_L$CO), 2.53 (1H, ddd, $J = 16.0, 6.0, 5.0$, CH$_G$$H_L$CO), 1.92 (2H, m, CH$_2$), 1.82 (2H, m, CH$_2$); ^{13}C NMR δ: 169.71 (s, CO), 132.39 (d, CH=), 119.35 (t, =CH$_2$), 62.68 (t, CH$_2$OSi), 62.47 (d, CHN), 45.75, 45.55 (t, each, 2×*C*H$_2$NCO), 40.11 (t, CH$_2$NTs), 34.95 (t, *C*H$_2$CO), 25.91, 24.28 (t each, 2×CH$_2$). Compound **10**: $[\alpha]_D = -27.3$ (*c* 1.9, $CHCl_3$); anal. calcd for $C_{25}H_{32}N_2O_4S$: C, 65.76; H, 7.06; N, 6.14; found: C, 65.68; H, 7.16; N, 6.11; ^{1}H NMR δ: 7.5–7.3 (5H, m, C$_6$H$_5$), 5.60 (1H, ddd, $J = 17.0, 11.0, 6.0$, CH=), 5.13 (1H, br d, $J = 11.0$, =CH_AH$_B$), 5.08 (1H, br d, $J = 17.0$, =CH_AH$_B$), 4.65 (1H, br q, $J = 6.0$, CHN), 4.51 (1H, d, $J = 12.0$, OCH_AH$_B$C$_6$H$_5$), 4.44 (1H, d, $J = 12.0$, OCH$_A$$H_BC_6H_5$), 3.63 (1H, dd, $J = 10.0, 7.0$, OCH_GH$_D$), 3.58 (1H, dd, $J = 10.0, 6.0$, OCH$_C$$H_D$), 3.48 (1H, ddd, $J = 15.0, 9.0, 6.0$, CH_EH$_F$NSO$_2$), 3.42 (1H, ddd, $J = 15.0, 9.0, 5.5$, CH$_E$$H_FNSO_2$), 3.37 (2H, br t, $J = 6.0$ Hz, CH$_2$N), 3.35 (1H, dt, $J = 10.5, 6.5$, CH_GH$_L$N), 3.23 (1H, dt, $J = 10.5, 6.0$, CH$_G$$H_L$CO), 2.76

(1H, ddd, $J=15.0$, 9.0, 6.0, CH_MH$_N$CO), 2.65 (1H, ddd, $J=15.0$, 9.0, 6.0, CH$_M H_N$CO), 2.01 (2H, m, CH_2), 1.99 (2H, m, CH_2). ^{13}C NMR δ: 169.55 (s, CON), 137.33 (s, C_6H_5), 133.40 (d, CH=), 128.30 (2×d, C_6H_5), 127.57 (3×d, C_6H_5), 118.93 (t, $=CH_2$), 72.86 (t, OCH_2), 70.47 (t, $OCH_2C_6H_5$), 59.28 (d, CHN), 46.38, 45.41 (t each, CH_2N), 40.95 (t, CH_2NSO_2), 36.38 (t, CH_2CO), 25.91 (t, CH_2), 24.32 (t, CH_2). Compound **11**: m.p. = 72–73°C; $[\alpha]_D=-6.4$ (*c* 0.9, $CHCl_3$); anal. calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.01; N, 3.63; found: C, 65.44; H, 6.02; N, 3.63; ^{1}H and ^{13}C NMR spectral data are in Table 2. Compound **12**: $[\alpha]_D=29.6$ (*c* 0.7, $CHCl_3$); anal. calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.01; N, 3.63; found: C, 65.37; H, 5.90; N, 3.55; ^{1}H and ^{13}C NMR spectral data are in Table 2. Compound **13**: $[\alpha]_D=95.3$ (*c* 1.1, $CHCl_3$); anal. calcd for $C_{21}H_{23}NO_5S$: C, 62.83; H, 5.77; N, 3.49; found: C, 62.77; H, 5.71; N, 3.44; ^{1}H NMR (CD_3COCD_3) δ: 7.77 (2H, d, $J=8.0$, $C_6H_4CH_3$), 7.42–7.20 (7H, m, C_6H_5+$C_6H_4CH_3$), 5.07 (1H, ddd, $J=6.5$, 3.5, 1.5, CHO), 3.89 (1H, dt, $J=5.0$, 3.5, CHN), 3.85 (1H, dd, $J=13.0$, 1.5, CH_AH$_B$N), 3.76 (1H, dd, $J=13.0$, 4.0, CH$_A H_B$N), 3.73 (1H, dd, $J=9.5$, 3.5, CHCH_CH$_D$O), 3.69 (1H, dd, $J=9.5$, 5.0, CHCH$_C H_D$O), 3.28 (1H, ddt, $J=9.5$, 6.5, 3.5, CH), 2.82 (1H, dd, $J=18.0$, 9.5, CH_EH$_F$CO), 2.43 (3H, s, $C_6H_4CH_3$), 2.27 (1H, dd, $J=18.0$, 3.5, CH$_E H_F$CO); ^{13}C NMR δ: 178.40 (s, CO), 144.49 (s, 4′-$C_6H_4SO_2$), 139.25 (s, C_6H_5), 134.04 (s, 1′-$C_6H_4SO_2$), 130.58 (2×d, 2′,6′-$C_6H_4SO_2$), 129.09 (2×d, C_6H_5), 128.30 (d, C_6H_5), 128.25 (2×d, 3′,5′-$C_6H_4SO_2$), 127.94 (2×d, C_6H_5), 83.71 (d, CHO), 73.76 (t, $OCH_2C_6H_5$), 73.08 (t, $CHCH_2O$), 66.86 (d, CHN), 55.12 (t, CH_2N), 43.36 (d, CHN), 34.83 (t, CH_2CO), 21.41 (q, CH_3).

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20. Batchmin of Macromodel Version 4.5 (Columbia Univ. New York), Amber* Force Field, united atoms, Monte Carlo stocastic algorithm with 5000 generated structures, minimization by PR conjugate gradient, energy window 12 kcal/mol. All the rotatable bonds were explored.
21. Structures generated by the conformational search were further optimized with the MMX force field (PC Model 4.0, Serena Software, Bloomington, IN). Energy comparison refers to MMX computed structures.