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Synthesis of Novel Acridino- and Phenazino-18-crown-6 Ligands and Their Optically Pure Dimethyl-substituted Analogues for Molecular Recognition Studies

Péter Huszthy*, Erika Samu[a], Borbála Vermes, Gabriella Mezey-Vándor, Mihály Nógrádi, Jerald S. Bradshaw[b] and Reed M. Izatt[b]

Research Group for Alkaloid Chemistry, Hungarian Academy of Sciences, H-1521 Budapest, Hungary
[a]Institute of Organic Chemistry, Technical University Budapest, H-1521 Budapest, Hungary
[b]Department of Chemistry, Brigham Young University, Provo Utah 84602, USA

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Abstract: Novel acridino- and phenazino-18-crown-6 ligands **5** and **6** were prepared from acridine-4,5-diol (**9**) and phenazine-1,9-diol (**10**) with tetraethylene glycol di-*p*-tosylate (**11**) using potassium *tert*-butoxide as a base in THF. New optically pure dimethyl-substituted acridino- and phenazino-18-crown-6 ligands (***R,R*)-7** and (***R,R*)-8** were also prepared by treating **9** and **10** with optically pure dimethyl-substituted tetraethylene glycol di-*p*-tosylate **[(*S,S*)-18]**. Molecular recognition studies on these novel ligands are underway. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Acridines; Crown ethers; Molecular recognition; Phenazines.

INTRODUCTION

Molecular recognition is a general phenomenon in nature. As examples, storage and retrieval of genetic information, enzyme–substrate interactions, immunological response, selective complexation and transport of metal ions across cell membranes by ionophore antibiotics or the metabolism of single enantiomeric forms of amino acids and sugars in biochemical pathways can be mentioned. Recent successes in imitating such natural phenomena using small synthetic compounds have shown that biological behaviour can be engineered into relatively simple molecules.

Crown ethers, for example, have demonstrated an ability to bind metal and organic cations strongly and selectively.[1-4] This has created interest in them as enzyme models.[5-8] The unique complexing characteristic of crown ethers containing oxygen atoms was first reported by Pedersen[9] more than three decades ago. Pedersen's discovery led to the synthesis and complexation studies of a great number and variety of macrocyclic compounds. The complexation properties of these host ligands have been reviewed.[1-4]

Enantiomeric recognition, as a special case of molecular recognition, involves the discrimination between

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enantiomers of the guest by a chiral host. Enantiomeric recognition of chiral organic ammonium salts by chiral crown ethers was first studied by Cram and coworkers.[10] Since their pioneering work, enantiomeric recognition of optically active ammonium salts by chiral crown ethers has received much attention.[11] Various structural changes to crown ether hosts have been made in attempts to enhance their complexation stability and selectivity. Some of these modifications have involved the insertion of heterocyclic units into the macroring.

We have prepared a number of chiral crown ether ligands containing pyridine derivatives[12-17] as part of the macroring, and studied their enantiomeric recognition with chiral organic ammonium salts by NMR spectroscopy[13-20], calorimetric titration[13,20-23] molecular mechanics calculation[14-16], Fourier transform ion cyclotron[24] and fast atom bombardment[25] mass spectrometry, X-ray crystallography,[13,26,27] solvent extraction,[28] chromatography,[29,30] circular dichroism spectroscopy,[31] and electrochemical methods.[32] These studies have established a tripod-like hydrogen bonding involving the pyridine nitrogen and two alternate oxygen atoms of the macrocycle and the three protons of the ammonium salt, π-π stacking between the pyridine ring of the ligand and the aromatic group of the ammonium salt, as well as steric repulsion between the bulky groups on the chiral positions of the macrocyle and the ammonium salt, respectively. We have also prepared and studied the enantiomeric recognition of chiral macrocycles containing phenanthroline[33] and pyrimidine[34] subcyclic units with the enantiomers of chiral organic ammonium salts by NMR spectroscopy. *Table 1* shows the degree of enantiomeric recognition (enantioselectivity) of some typical representatives of known dimethyl-substituted optically pure chiral crown ether ligands **[(*S,S*)-1–(*S,S*)-4]** (see *Figure 1*) toward the enantiomers of α-(1-naphthylethyl)ammonium perchlorate (NapEt) expressed in Δlog *K* values. (*K* represents the stability constant of a chiral ligand-enantiomeric salt complex).

Table 1. Log *K* and Δlog *K* values for the complexation of dimethyl-substituted chiral macrocycles with (*R*)- and (*S*)-α-(1-naphthyl)ethylammonium perchlorate (NapEt) as determined by ^{1}H NMR method at 25°C in $CDCl_3/CD_3OD$ (1/1)[a]

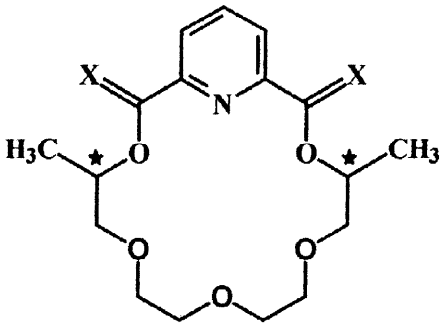
Ligand	Ammonium salt	log *K*	Δlog *K*	Ligand	Ammonium salt	log *K*	Δlog *K*
(*S,S*)-1	(*R*)-NapEt	3.96[b]	0.54[b]	**(*S,S*)-3**	(*R*)-NapEt	4.56[d]	0.40[d]
	(*S*)-NapEt	3.42[b]			(*S*)-NapEt	4.16[d]	
(*R,R*)-2	(*R*)-NapEt	2.20[c]	0.60[c]	**(*S,S*)-4**	(*R*)-NapEt	5.18[e]	0.95[e]
	(*S*)-NapEt	2.80[c]			(*S*)-NapEt	4.23[e]	

[a]Data taken from literature: [b]ref 19, [c]ref 20, [d]ref 33 and [e]ref 34.

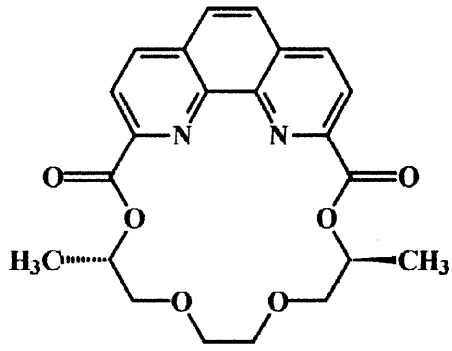
The present paper focusses on the synthesis of members of a new class of macrocycles **[5–(*R,R*)-8]** containing an acridine and a phenazine unit, respectively (see *Figure 1*). These new ligands are promising candidates for strong and selective complexation of both metal and organic ammonium ions. In addition, chiral ligands **(*R,R*)**-7 and **(*R,R*)-8** are very likely to show selectivity toward enantiomers of chiral organic ammonium salts containing an aromatic ring. The tricyclic ring system imparts higher rigidity to the upper part of the

molecule, *i.e.* close to the chiral centers. Also the more extended π-systems of phenazine and acridine provide stronger π–π interactions with a guest containing an aromatic ring. Both features assist enantioselectivity.[33,35] Another important advantage of these novel ligands is that they have chromophore systems which allow us to study their complexation using UV-visible spectroscopy.[11]

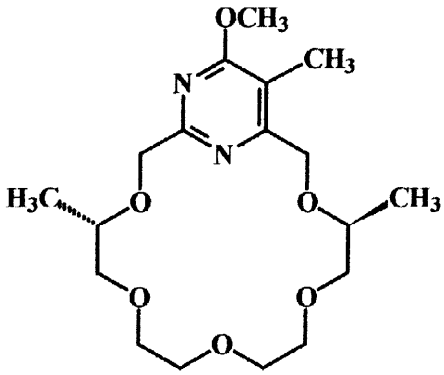
Complexation studies on these new ligands with both metal and organic ammonium ions are in progress.



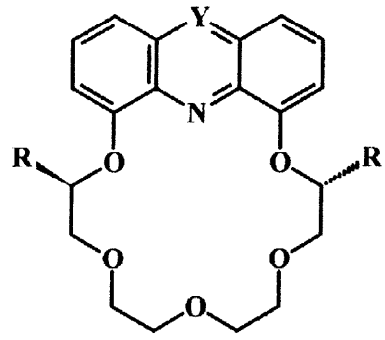
(*S,S*)-1: X = H_2
(*R,R*)-2: X = O



(*S,S*)-3



(*S,S*)-4

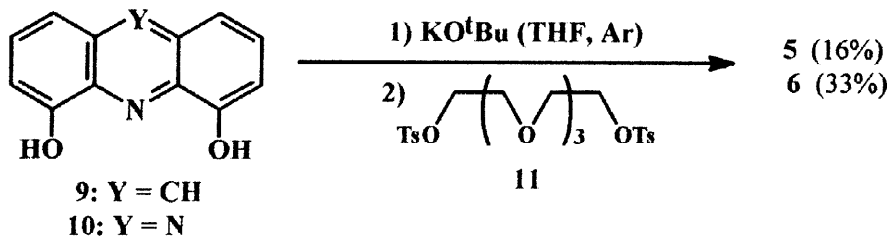


5: R = H, Y = CH
6: R = H, Y = N
(*R,R*)-7: R = CH_3, Y = CH
(*R,R*)-8: R = CH_3, Y = N

Figure 1. **Structures of 18-crown-6 type ligands containing heterocyclic units**

RESULTS AND DISCUSSION

The achiral acridino-18-crown-6 ligand (**5**) was prepared from acridine-4,5-diol[36] (**9**) and tetraethylene glycol di-*p*-tosylate[37] (**11**) using potassium *tert*-butoxide as a base in THF. Ligand **6**, the phenazino-analogue of **5**, was obtained in the same way starting from phenazine-1,9-diol[38] (**10**) (see *Scheme 1*). The ^{1}H NMR spectrum of **6** showed a broad singlet at δ = 2.80 (2 H) and its IR spectrum a broad band between 3650 and 3150 cm^{-1} indicating that **6** contained one molecule of water which was also confirmed by elemental analysis. This water was firmly bound as shown by the fact that it could not be removed by heating at 80 °C over phosphorus pentoxide in a vacuum oven overnight. We note here that phenanthrolino-macrocycle (*S,S*)-**3** also complexes water as confirmed by X-ray analysis.[33]



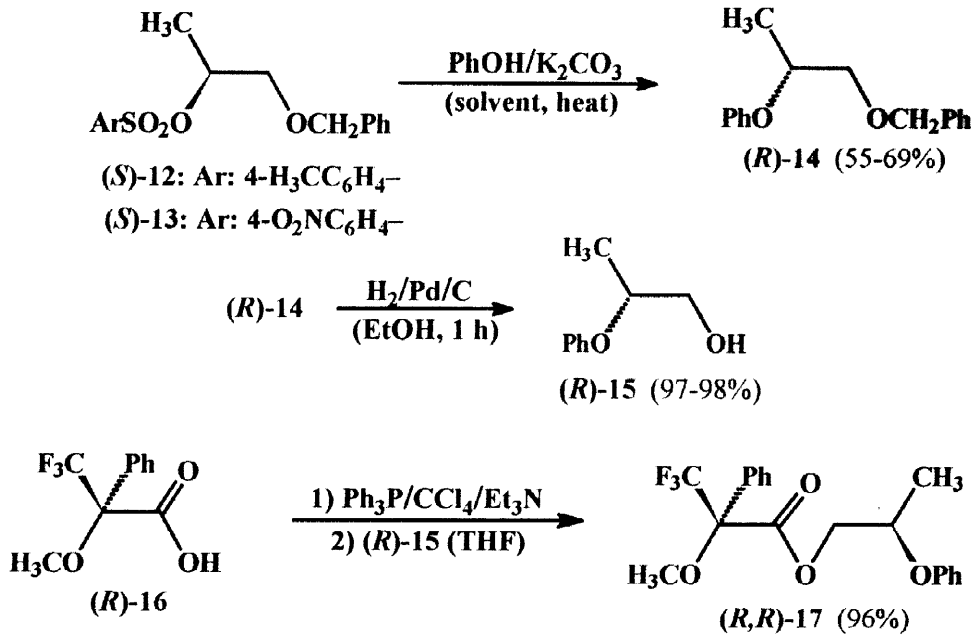
9: Y = CH
10: Y = N

Scheme 1. **Preparation of new achiral ligands**

Our earlier studies on the factors governing enantiomeric recognition of chiral organic ammonium salts by chiral pyridino-18-crown-6 ligands showed that the highest enantioselectivity can be expected when the chiral centers bearing the alkyl groups in the ligand are as close to the heteroaromatic unit as possible.[20,35] Therefore we turned to the synthesis of the chiral ligands **(*R,R*)-7** and **(*R,R*)-8** starting from diols **9** and **10** and a chiral secondary arylsulfonate such as **(*S,S*)-18**. In this case, however, the method used for obtaining **5** and **6** failed, probably because of the greater tendency for the elimination of the chiral secondary tosylate **(*S,S*)-18** compared to the primary tosylate **11.** Securing optical purity of the ligands, *i.e.* complete inversion of configuration, involved further problems and required careful optimisation of reaction conditions. The situation was entirely different from our earlier syntheses of chiral macrocycles where reactions did not occur at the chiral centers of the precursors. Therefore model experiments using the optically pure sulfonates **(*S*)-12** and **(*S*)-13** and phenolate generated by K_2CO_3, a weak base, were carried out (see *Scheme 2*).

p-Tosylate and 4-nitrobenzenesulfonate were selected as leaving groups in the substrates **(*S*)-12** and **(*S*)-13**. *N,N*-Dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and hexamethylphosphoramide (HMPA), all known to favour S_N2 reactions, were used as solvents. We also checked the influence of the temperature. The results of model experiments are summarised in *Table 2*. It can be seen (entries 1 and 2) that the tosylate leaving group both in DMF and DMSO caused total inversion of configuration. However, in the case of **(*S*)-13**, incorporating the better leaving group 4-nitrobenzenesulfonate and using HMPA as a solvent, almost total racemization occurred (entry 7). Entries 3 and 4 indicate that raising the temperature favours racemization. The model compounds (*i.e.* the arenesulfonates **(*S*)-12**[39,40] and **(*S*)-13**) were prepared from (S)-(+)-1-benzyloxypropan-2-ol[39] using the corresponding arenesulfonyl chlorides and powdered KOH in THF, a well established method in our laboratories.[14-16,29,30]

Enantiomeric excess (e.e.) values for **14** and **15** were determined by polarimetry (see *Table 2*). For entries 1, 3 and 4 e.e. values for propanols **15** were also determined by ^{1}H NMR spectroscopy after conversion to their Mosher's esters.[41] Surprisingly the ^{1}H NMR spectra of Mosher's esters **17** obtained from optically impure propanols **15** did not show even at 500 MHz clear separation of any signals, but merely a shoulder at δ = 3.52 merged into the singlet at δ = 3.51 for the methoxy protons when taken in $CDCl_3$, while in C_6D_6 the



Scheme 2. **Reaction of model compounds with potassium phenoxide, debenzylation of the products and Mosher's ester formations from the resulting alcohols**

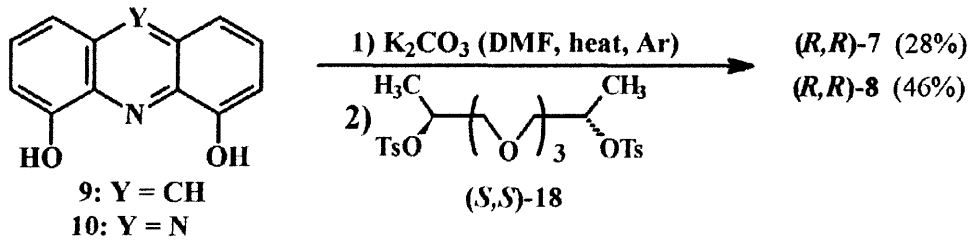
Table 2. Transformation of (*S*)-1-benzyloxy-2-arylsulfonyloxypropanes (*S*)-**12** and (*S*)-**13** into 1-benzyloxy-2-phenoxypropane (**14**)[a] followed by removal of the benzyl group by catalytic hydrogenation to give 2-phenoxypropan-1-ol **15**[a] (see also *Scheme 2*).

Entry	Starting material	Solvent (temp. [°C])	Reaction time (h)	Yield of **14** (%)	$[\alpha]_D^{20}$ of **14**[a,b] [e.e. (%)]	Yield of **15** (%)	$[\alpha]_D^{20}$ of **15**[a,c] [e.e. (%)]
1	(*S*)-**12**	DMF (50)	44	68	+5.58 (100)	97	–37.99 (100)
2	(*S*)-**12**	DMSO (50)	35	65	+5.57 (100)	98	–37.95 (100)
3	(*S*)-**12**	HMPA (50)	120	64	+3.68 (66)	98	–24.58 (65)
4	(*S*)-**12**	HMPA (90)	18	69	+1.95 (35)	97	–13.71 (36)
5	(*S*)-**13**	DMF (50)	32	61	+5.25 (94)	98	–35.66 (94)
6	(*S*)-**13**	DMSO (50)	16	55	+4.57 (82)	97	–30.75 (81)
7	(*S*)-**13**	HMPA (50)	108	62	+0.027 (0.5)	97	–0.23 (0.6)

[a]Predominant configuration *R*. [b][c = 10, THF], [c][c = 0.9, MeOH]

$\underline{CH_3}C(H)$ protons gave well separated doublets centered at $\delta = 0.83$ ($J = 6$ Hz) and $\delta = 0.89$ ($J = 6$ Hz) which could be used for the determination of the e.e. values. The ^1H NMR spectrum of the Mosher's ester obtained from propanol (*R*)-**15** (see entry 1) showed no shoulder at $\delta = 3.52$ only a sharp singlet at $\delta = 3.51$ in $CDCl_3$ and a single doublet centered at $\delta = 0.83$ in C_6D_6 confirming that the optical rotation measured for this sample corresponded to 100% e.e. We note that our maximum value for (*R*)-**15** (measured at the reported temperature and wavelength in the same solvent) were much higher $\{[\alpha]_{578}^{25} = -39.7°$ ($c = 0.9$, MeOH)$\}$ than that reported $\{[\alpha]_{578}^{25} = -30°$ (c not given, MeOH)$\}$.[42]

Instead of the conventional method involving the separate preparation of the acid chloride, [41] the Mosher's esters were obtained directly from Mosher's acid [(*R*)-**16**] and propanol **15** using triphenylphosphine, carbon tetrachloride and triethylamine in THF, *i.e.* first the acid chloride was generated *in situ* which then reacted with the alcohol under basic conditions (see *Scheme 2*).

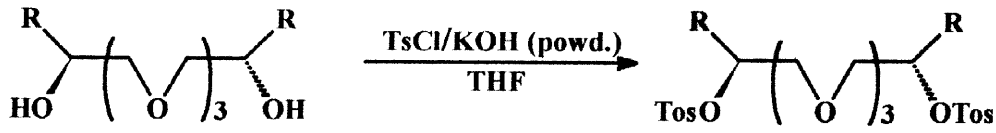


Scheme 3. **Preparation of new dimethyl-substituted chiral ligands**

Based on the results of the above model experiments, we prepared the new dimethyl-substituted chiral ligands (*R,R*)-**7** and (*R,R*)-**8** from diols **9** and **10** using ditosylate (*S,S*)-**18** and K_2CO_3 as a base in DMF at 50 °C (see *Scheme 3*). The primary products of these reactions were the potassium tosylate complexes, which crystallised from EtOAc in a pure state. Free ligands were obtained by decomplexing the products by chromatography on alumina. Based on the above mentioned model experiments, we believe that chiral ligands (*R,R*)-**7** and (*R,R*)-**8** were formed by total inversion of configuration and were optically pure. This supposition was confirmed by the fact that melting points and optical rotations did not change on recrystallization. Also their ^{1}H-and ^{13}C NMR spectra lacked signals diagnostic of *meso* compounds, which should have been formed if some degree of racemization had occurred.

Improved procedures were elaborated for the preparation of acridin-4,5-diol[36] (**9**) and phenazin-1,9-diol[38] (**10**). The 1,6- and 1,9-dinitrophenazines obtained as a mixture by nitration of phenazine[43] were separated by crystallisation and not by chromatography as described in the literature[43]. Catalytic hydrogenation of 1,9-dinitrophenazine gave purer 1,9-diaminophenazine with a better yield than reduction with zinc in acetic acid as recommended.[43] Also for the preparation of diol **9** from 4-amino-5-methoxyacridine[36]– especially on a larger scale – using phosphoric acid at 180 °C under Ar and at atmospheric pressure was a more efficient and convenient method than heating in concentrated hydrochloric acid in a sealed tube.[36] We prepared diol **10** from 1,9-diaminophenazine in the same manner as **9** from 4-amino-5-methoxyacridine.

Tetraethylene glycol di-*p*-tosylates **11**[37] and (*S,S*)-**18** were made from diols **19** and (*S,S*)-**20**[44] as outlined in *Scheme 4* by a method well established in our laboratories.[14-16,29,30] As no IR, ^{1}H - and ^{13}C NMR spectral data have been reported for diols **9** and **10** we include them here. We also report TLC data for all compounds.



19: R = H
(*S*,*S*)-20: R = CH_3

11: R = H (91%)
(*S*,*S*)-18: R = CH_3 (81%)

Scheme 4. **Preparation of ditosylates for the new ligands**

EXPERIMENTAL

Infrared spectra were obtained on a Zeiss Specord IR 75 spectrometer. Optical rotations were taken on a Perkin-Elmer 241 polarimeter that was calibrated by measuring the optical rotations of both enantiomers of menthol.

^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra were taken on a Bruker DRX-500 Avance spectrometer in $CDCl_3$ unless otherwise indicated. Molecular weights were determined by a VG-ZAB-2 SEQ reverse geometry mass spectrometer. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, L. Eötvös University, Budapest, Hungary. Melting points were taken on a Boetius micro melting point apparatus and were uncorrected. Starting materials were purchased from Aldrich Chemical Company unless otherwise noted. Silica gel 60 F_{254} (Merck) and aluminum oxide 60 F_{254} neutral type E (Merck) plates were used for TLC. Aluminum oxide (neutral, activated, Brockman I) and silica gel 60 (70-230 mesh, Merck) were used for column chromatography. Solvents were dried and purified according to the well established methods.[45] Evaporations were carried out under reduced pressure unless otherwise stated.

2,5,8,11,14-Pentaoxa-26-azatetracyclo[13.9.3.0.^{19,27}0^{21,25}]heptacosa-15,17,19,21,22,24(1),26-heptaene (5). To a well stirred mixture of potassium *tert*-butoxide (449 mg, 4 mmol) in THF (2 mL) was added dropwise at -15 °C and under Ar acridine-4,5-diol (**9**) (422 mg, 2 mmol) dissolved in THF (30 mL). The reaction mixture was stirred at -15 °C for 15 min, at rt for 30 min, then it was cooled to -15°C and ditosylate **11** (1.05 g, 2 mmol) dissolved in THF (30 mL) was added. The reaction mixture was stirred at -15°C for 15 min and at rt for 20 h. The solvent was evaporated at rt, and the residue was taken up in ice-water (20 mL) and extracted with CH_2Cl_2 (30+3x20 mL). The combined organic extracts were shaken with distilled water (40 mL), dried over $MgSO_4$, filtered and the solvent removed. Chromatography on alumina using first 5% then 10% EtOH in toluene as eluents and recrystallization from CH_2Cl_2-ether mixture gave pale yellow crystals (120 mg, 16 %). R_f = 0.32 (alumina TLC, 18% EtOH in toluene); m. p.: 104-106 °C; IR (KBr) ν_{max} 3180, 3150, 3080, 3060, 3030, 3010, 2960, 2950, 2930, 2880, 2850, 1630, 1560, 1460, 1440, 1400, 1350, 1320, 1230, 1110, 1100, 970, 900, 750, 720 cm^{-1}; ^1H NMR δ 3.86-3.87 (m, 4 H), 3.95-3.96 (m, 4 H), 4.17-4.19 (m, 4 H), 4.39-4.40 (m, 4 H), 6.96 (d, J = 8 Hz, 2 H), 7.40 (t, J = 8 Hz, 2 H), 7.52 (d, J = 8 Hz, 2 H), 8.63 (s, 1 H); ^{13}C NMR δ 68.93,

68.98, 70.33, 71.80, 107.08, 119.74, 126. 03, 127.88, 135.10, 141.07, 154.96. **MS (FAB, glycerol matrix) 370** $[M+H]^+$. Anal. Calcd. for $C_{21}H_{23}NO_5$: C, 68.26; H, 6.28; N, 3.79. Found: C, 68.11; H, 6.32; N, 3.78.

2,5,8,11,14-Pentaoxa-20,26-diazatetracyclo[13.9.3.0.^{19,27}0^{21,25}]heptacosa-15,17,19,21,22,24(1),26-heptaene (6). Compound **6** was prepared as described above for compound **5** starting from phenazine-1,9-diol (**10**) (424 mg, 2 mmol), potassium *tert*-butoxide (449 mg, 4 mmol), ditosylate **11,** (1.05 g, 2 mmol) and THF (30 mL). Chromatography on alumina using 10% EtOH in toluene as an eluent and recrystallization from EtOH gave yellow crystals (260 mg, 33 %). R_f = 0.44 (alumina TLC, 18% EtOH in toluene); m. p.: 155-157 °C; IR (KBr) ν_{max} 3650-3150 (broad), 3140, 3130, 3110, 3080, 3050, 3010, 2970, 2960, 2950, 2930, 2890, 2850, 2820, 1650, 1630, 1600, 1570, 1540, 1490, 1460, 1420, 1350, 1330, 1280, 1270, 1110, 960, 950, 900, 830 ,750, 730, 620, 550 cm^{-1}; ^{1}H NMR δ 2.80 (s, broad, 2 H), 3.81-3.83 (m, 4 H), 3.89-3.91 (m, 4 H), 4.12-4.14 (m, 4 H), 4.38-4.40 (m, 4 H), 6.98 (d, J = 8 Hz, 2 H), 7.70 (t, J = 8 Hz, 2 H), 7.77 (d, J = 8 Hz, 2 H); ^{13}C NMR δ 68.79, 69.05, 70.09, 71,44, 106.80, 121.05, 130.91, 135.67, 144.20, 154.85; MS (FAB, glycerol matrix) 371 $[M+H]^+$. Anal. Calcd. for $C_{20}H_{22}N_2O_5$ x H_2O: C, 61.84; H, 6.22; N, 7.21. Found: C, 62.05; H, 6.13; N, 7.41.

(3*R*,13*R*)-(-)-Dimethyl-2,5,8,11,14-pentaoxa-26-azatetracyclo[13.9.3.0.^{19,27}0^{21,25}]heptacosa-15,17,19,21,22-24(1),26-heptaene [(*R,R*)-7)]. A mixture of acridine-4,5-diol (**9**) (455 mg, 2.15 mmol), ditosylate (***S,S*)-18** (1.14 g, 2.15 mmol), finely powdered anhydrous K_2CO_3 (2.97 g, 21.5 mmol) and DMF (38 mL) was stirred under Ar at rt for 10 min then at 50 °C for 5 days. The solvent was removed at 45 °C and the residue was taken up in a mixture of ice-water (60 mL) and EtOAc (120 mL). The aqueous phase was extracted with EtOAc (4x60 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solution was concentrated to 20 mL. After standing at rt for 4 h and in a refrigerator for 12 h, the crystals were filtered off, washed with a small amount of EtOAc to give the potassium tosylate complex (383 mg, 29%) as pale yellow crystals. R_f = 0.44 (alumina TLC, 9% EtOH in toluene); $[\alpha]_D^{25}$ = -3.45° (c = 0.52, CH_2Cl_2); M. p.: 239-40 °C (EtOAc); IR (KBr) ν_{max} 3030, 2970, 2940, 2900, 2880, 2850, 1660, 1620, 1550, 1450, 1400, 1360, 1310, 1280, 1220, 1200, 1110, 1100, 1030, 1000, 920, 760, 680, 560 cm^{-1}; ^{1}H NMR δ 1.50 (d, J = 6 Hz, 6 H), 2.14 (s, 3 H), 3.63-3.70 (m, 6 H), 3.91-3.96 (m, 4 H), 4.28-4.30 (m, 2 H), 4.84-4.86 (m, 2 H), 6.75 (d, J = 8 Hz, 2 H), 7.02 (d, J = 8 Hz, 2 H), 7.41 (t, J = 8 Hz, 2 H), 7.53 (d, J = 8 Hz, 2 H), 7.56 (d, J = 8 Hz, 2 H), 8.67 (s, 1 H); ^{13}C NMR δ 14.78, 21.29, 69.52, 70.91, 73.36, 73.43, 109.15, 120.63, 126.03, 128.16, 128.36, 129.17, 136.85, 138.48, 141.22, 144.17, 152.59. The complex was chromatographed on alumina using 2% EtOH in toluene as an eluent to give **(*R,R*)-7** (243 mg, 97%) as pale yellow crystals. R_f = 0.44 (alumina TLC, 9% EtOH in toluene); $[\alpha]_D^{25}$ = -70.68° [c = 0.88, CH_2Cl_2]; m. p.: 93-4 °C (toluene); IR (KBr) ν_{max} 3030, 2970, 2920, 2880, 2860, 2830, 1650, 1620, 1550, 1510, 1450, 1390, 1360, 1310, 1280, 1120, 1100, 990, 920, 850, 750, 650 cm^{-1}; ^{1}H NMR δ 1.48 (d, J = 6 Hz, 6 H), 3.72-4.07 (m, 12 H), 5.17-5.21 (m, 2 H), 7.11 (d, J = 8 Hz, 2 H), 7.40 (t, J = 8 Hz, 2 H), 7.55 (d, J = 8 Hz, 2 H), 8.65 (s, 1 H); ^{13}C NMR δ 16.04, 67.21, 71.38, 74.67,

75.02, 98.28, 112.24, 120.43, 125.92, 135.30, 141.85, 153.82; MS (FAB, glycerol matrix) 398 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.25; H, 6.87; N, 3.58.

(3*R*,13*R*)-(-)-Dimethyl-2,5,8,11,14-pentaoxa-20,26-diazatetracyclo[13.9.3.0.^{19,27}0^{21,25}]heptacosa-15,17,19-21,22,24(1),26-heptaene [(*R,R*)-8)]. Compound **(*R,R*)-8** was prepared as described above for compound **(*R,R*)-7** starting from phenazine-1,9-diol (**10**) (1.06 g, 2 mmol). First the potassium tosylate complex of **(*R,R*)-8** was obtained (572 mg, 47%); R_f = 0.51 (alumina TLC, 9% EtOH in toluene); $[\alpha]_D^{25}$ = +16.63° [c = 0.481, CH_2Cl_2]; m. p.: 209-10 °C (EtOAc); IR (KBr) ν_{max} 3030, 2960, 2900, 2870, 2850, 1660, 1620, 1580, 1550, 1510, 1480, 1440, 1400, 1380, 1330, 1300, 1280, 1250, 1210, 1190, 1100, 1030, 1000, 900, 800, 750, 730, 670, 530 cm^{-1}; ^1H NMR δ 1.51 (d, J = 6 Hz, 6 H), 2.11 (s, 3 H), 3.62-3.72 (m, 6 H), 3.86-3.95 (m, 4 H), 4.28-4.30 (m, 2 H), 4.88-4.90 (m, 2 H), 6.64 (d, J = 8 Hz, 2 H), 7.09 (d, J = 8 Hz, 2 H), 7.38 (d, J = 8 Hz, 2 H), 7.76 (t, J = 8 Hz, 2 H), 7.83 (d, J = 8 Hz, 2 H); ^{13}C NMR δ 14.75, 21.25, 69.68, 70.95, 73.30, 74.09, 109.11, 120.50, 125.70, 128.09, 132.02, 135.64, 138.79, 143.16, 143.56, 152.73. Decomplexation as described above gave **(*R,R*)-8** as yellow crystals (367 mg, 98%). R_f = 0.51 (alumina TLC, 9% EtOH in toluene); $[\alpha]_D^{25}$ = -121.5° (c = 0.521, CH_2Cl_2); m. p.: 162-3 °C (EtOH). IR (KBr) ν_{max} 3060, 3050, 3030, 3020, 3010, 2950, 2920, 2900, 2860, 2850, 2830, 1600, 1580, 1530, 1460, 1390, 1370, 1360, 1320, 1300, 1260, 1230, 1100, 970, 900, 810, 730 cm^{-1}; ^1H NMR δ 1.49 (d, J = 6 Hz, 6 H), 3.72-4.06 (m, 12 H), 5.08-5.11 (m, 2 H), 7.12 (d, J = 8 Hz, 2 H), 7.72 (t, J = 8 Hz, 2 H), 7.80 (d, J = 8 Hz, 2 H); ^{13}C NMR δ 15.79, 71.39, 71.59, 74.53, 75.74, 111.15, 121.60, 130.83, 136.64, 144.29, 154.00; MS (FAB, glycerol matrix) 399 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.25; H, 6.55; N, 6.98.

Acridine-4,5-diol (9). A stirred mixture of 4-amino-5-methoxy-acridine[36] (2.24 g, 10.0 mmol) and 70% (w/w) aqueous H_3PO_4 (50 mL) was stirred in an oil bath under Ar at 180 °C for 5 days. The reaction mixture was cooled to rt, poured on ice (40 g) and its p*H* was adjusted to 7 with solid NaOAc. The hardly soluble product was extracted with EtOAc (1x400 and 3x200 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated. The crude product was recrystallized from boiling toluene using charcoal to give pure acridine-4,5-diol (**9**) (1.57 g, 74%). R_f = 0.3 (silica gel TLC 5% MeOH in CH_2Cl_2); m. p.: 266-7 °C (toluene); (lit.[36] m. p.: 265-7 °C (aqueous EtOH)); IR (KBr) ν_{max} 3410, 3030, 2970, 2930, 2850, 1630, 1570, 1520, 1470, 1430, 1360, 1340, 1240, 1220, 1170, 1100, 1020, 940, 900, 860, 740, 710, 620, 530, 470 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.12 (d, J = 8 Hz, 2 H), 7.47 (t, J = 8 Hz, 2 H), 7.57 (d, J = 8 Hz, 2 H), 8.97 (s, 1 H), 10.19 (broad s, 2 H); ^{13}C NMR (DMSO-d_6) δ 108.93, 117.70, 127.03, 127.15, 135.52, 138.22, 152.83.

1,9-Dinitrophenazine and 1,6-dinitrophenazine. Nitration of phenazine (9.0 g, 50 mmol) gave 13 g, (96 %) of a mixture of isomers which was finely powdered and stirred vigorously with boiling AcOH (390 mL) for 4 h. The insoluble part was filtered off hot and was dried to give pure 1,6-dinitrophenazine (3.8 g, 28%). R_f = 0.65 (silica gel, 11% EtOAc in toluene); m.p.: 344-345 °C (AcOH), (lit.[43] m.p.: 343 °C (AcOH)). The filtrate was boiled until a clear solution formed, cooled very slowly and stored at room temperature for 2 days. The crystals

were filtered off. Concentration of the mother liquor to one fifth of its original volume at atmospheric pressure gave a second crop of crystals. The first and second crops were combined, dried and recrystallized from boiling toluene using charcoal to give pure 1,9-dinitrophenazine (5.6 g, 41%). R_f = 0.27 (silica gel, 11% EtOAc in toluene); m.p.: 267-268 °C (toluene), (lit.[43] m.p.: 273 °C (EtOH)).

1,9-Diaminophenazine. To a stirred mixture of finely powdered 1,9-dinitrophenazine (2.0 g, 7.4 mmol) and 10% palladium on charcoal catalyst (0.4 g) EtOH (350 mL) was added under Ar. Ar was replaced by hydrogen and hydrogenation was carried out in the ususal way at rt and atmospheric pressure to give the diamine (1.53 g, 98%) as dark red crystals. R_f = 0.23 (silica gel TLC, 33% EtOAc in toluene); m.p.: 263-264 °C, (lit.[43] m.p.: 264-265 °C).

Phenazine-1,9-diol (10). This compound was prepared in the same way as described above for acridine-4,5-diol (**9**) starting from 1,9-diamino-phenazine[43] (3.7 g, 17.6 mmol). The crude product (2.9 g,, 78%) was recrystallized from boiling toluene using charcoal to give pure **10** (2.2 g, 59%); R_f = 0.45 (silica gel TLC 9% MeOH in CH_2Cl_2); m. p.: 296 °C. (toluene), (lit.[38] m. p.: 296 °C (benzene)); IR (KBr) ν_{max} 3550, 3080, 3030, 3010, 2950, 2920, 2900, 2850, 1660, 1640, 1620, 1570, 1530, 1490, 1470, 1440, 1370, 1290, 1220, 1170, 1100, 1030, 900, 830, 760, 560 cm^{-1}; ^1H NMR (DMSO-d_6/$CDCl_3$, 1:1) δ 7.09 (d, J = 8 Hz, 2 H), 7.61 (d, J = 8 Hz, 2 H), 7.73 (t, J = 8 Hz, 2 H), 10.20 (broad s, 2 H); ^{13}C NMR (DMSO-d_6/$CDCl_3$,1:1) δ 108.68, 118.28, 132.17, 132.58, 143.48, 153.21.

3,6,9-Trioxaundecane-1,10-diol di-*p*-tosylate (tetraethylene glycol di-*p*-tosylate) (11). To a well stirred mixture of finely powdered KOH (27.9 g, 85%, 0.423 mol) in THF (50 mL) was added dropwise at -30 °C and under Ar tetraethylene glycol (**19**) (10.1 g, 0.052 mol) and tosyl chloride (26.8 g, 0.14 mol) dissolved together in THF (200 mL). The resulting mixture was stirred at -30 °C for 30 min, at -20 °C for 1 h, then it was allowed to warm up to rt and stirring was continued at rt for 2 h. The solvent was evaporated at rt and the residue taken up in ice-water (300 mL) and CH_2Cl_2 (600 mL). The aqueous phase was extracted with CH_2Cl_2 (3x200 mL). The combined organic phase was shaken with distilled water (400 mL), dried ($MgSO_4$), filtered and evaporated. Chromatography on silica gel using 8% EtOH in toluene as an eluent gave **11** (23.8 g, 91 %) as a colourless oil identical in every aspect to that prepared by the literature procedure.[37]

(*S*)-(-)-(2-Benzyloxy-1-methyl)ethyl 4-methyl-benzenesulfonate [(*S*)-12]. Compound **(*S*)-12** was prepared as described above for compound **11** starting from (*S*)-(+)-1-benzyloxypropan-2-ol,[39,40] (17.3 g, 0.104 mol), finely powdered KOH (27.9 g, 85%, 0.423 mol), tosyl chloride (26.8 g, 0.14 mol) and THF (250 mL). Chromatography on silica gel using 15% EtOAc in hexane as an eluent gave **(*S*)-12** (27.2 g, 81 %) which solidified on standing; R_f = 0.52 (silica gel TLC, 25% EtOAc in hexane); $[\alpha]_D^{25}$ = -7.04° [c = 0.19, $CHCl_3$], (lit.[40] $[\alpha]_D^{25}$ = -6.34° [c = 0.19, $CHCl_3$]); m. p.: 29-30 °C, (lit.[40] m. p.: 33 °C).

(*S*)-(+)-(2-Benzyloxy-1-methyl)ethyl 4-nitro-benzenesulfonate [(*S*)-13]. Compound **(*S*)-13** was prepared as described above for compound **(*S*)-12** starting from (*S*)-(+)-1-benzyloxypropan-2-ol[39,40] (8.65 g, 0.052 mol),

and 4-nitrobenzenesulfonyl chloride (15.53 g, 0.070 mol). The crude product was recrystallized from ether to give pale yellow crystals (10.2 g, 56 %). R_f = 0.46 (silica gel TLC, 25% EtOAc in hexane); $[\alpha]_D^{25}$ = +21.91° (c = 2.31, THF); m. p.: 85-86 °C (ether); IR (KBr) ν_{max} 3110, 3080, 3070, 3030 3010, 2960, 2930, 2890, 2870, 2820, 1620, 1600, 1540, 1520, 1490, 1460, 1400, 1360, 1340, 1300, 1180, 1170, 1100, 1070, 980, 920, 900, 840, 770, 760, 740, 720, 690, 670, 610, 600, 550 cm^{-1}; ^1H NMR δ 1.41 (d, J = 6 Hz, 3 H), 3.44-3.53 (m, 2 H), 4.28-4.36 (m, 2 H), 4.85-4.90 (m, 1 H), 7.10-7.29 (m, 5H), 8.02 (d, J = 9 Hz, 2 H), 8.13 (d, J = 9 Hz, 2 H); ^{13}C NMR δ 17.89, 72.43, 73.27, 80.43, 123.97, 127.70, 128.06, 128.38, 129.10, 137.17, 142.84, 150.33. Anal. Calcd. for $C_{16}H_{17}NO_6S$: C, 54.69; H, 4.88; S, 9.12. Found: C, 54.73; H, 5.05; S, 9.27.

General procedure for the transformation of (*S*)-12 and (*S*)-13 into (2-benzyloxy-1-methyl)ethyl phenyl ether (14). A mixture of **(*S*)-12** (3.20 g, 10 mmol) or **(*S*)-13** (3.51 g, 10 mmol), phenol (0.99 g, 10.5 mmol), finely powdered anhydrous K_2CO_3 (2.9 g, 21 mmol) and a solvent (18 mL) was stirred at the temperature and for the time shown in *Table 2*. The solvent was evaporated at 50 °C and the residue taken up in ice-water (60 mL) and ether (100 mL). The aqueous phase was extracted with ether (3x50 mL). The combined organic extracts were shaken with 20 % aqueous KOH (2x50mL), distilled water (1x50 mL), saturated sodium chloride solution (2x50 mL), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated . The crude product was purified by column chromatography on silica gel using 1.6 % acetone in hexane as an eluent. Yields, optical rotations and e.e. values are given in *Table 2*. R_f = 0.45 (silica gel TLC, 2.4 % acetone in hexane); IR (neat) ν_{max} 3080, 3060, 3030 2970, 2930, 2860, 2840, 1590, 1580, 1490, 1440, 1360, 1290, 1280, 1230, 1170, 1140, 1100, 1010, 980, 930, 870, 790, 780, 740, 690 cm^{-1}; ^1H NMR δ 1.32 (d, J = 6 Hz, 3 H), 3.52-3.67 (m, 2 H), 4.54-4.59 (m, 3 H), 6.91-6.93 (m, 3 H), 7.23-7.34 (m, 7H); ^{13}C NMR δ 17.63, 73.54, 73.73, 73.88, 116.54, 121.33, 128.09, 128.11, 128.84, 129.93, 138.72, 158.42. Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.16; H, 7.26.

Determination of the enantiomeric excess values for ether 14. E.e. values (see *Table 2*) were determined by comparing their optical rotation to that of an optically pure sample of **(*R*)-14** prepared under conditions shown in entry 1 (*Table 2*) {$[\alpha]_D^{20}$ = +5.58° [c = 10.00, THF]}. Debenzylation of this product by catalytic hydrogenation gave **(*R*)-15** of 100% e.e. as proved with the help of its (*R*)-(+)-MTPA ester **[(*R,R*)-17]** by ^1H NMR spectroscopy.[41]

2-Phenoxypropane-1-ol (15). Hydrogenation of benzyl ether **14** (1.0 g, 4.13 mmol) in EtOH (45 mL) over 10% palladium on charcoal (0.1 g) for 1 h gave after the usual work-up and chromatography on silica gel using 20% acetone in hexane as an eluent propanol **15**. Yields, optical rotations and e.e. values are given in Table 2. R_f = 0.31 (silica gel TLC, 20 % acetone in hexane); IR (neat) ν_{max} 3700-3100 (broad), 3070, 3040, 3020 2990, 2930, 2870, 1600, 1590, 1500, 1470, 1380, 1300, 1240, 1180, 1140, 1110, 1080, 1050, 990, 920, 880, 770, 700. cm^{-1}; ^1H NMR δ 1.23 (d, J = 6 Hz, 3 H), 2.50 (s, broad, 1 H), 3.66-3.72 (m, 2 H), 4.42-4.48 (m, 1 H), 6.90-6.95 (m, 3 H), 7.22-7.27 (m, 2 H); ^{13}C NMR δ 15.77, 66.11, 74.69, 116.09, 121.12, 129.51, 157.66.

Determination of the e.e. values for propanol 15. E.e. values for **15** (see *Table 2*) were determined by comparison of their optical rotations to that of optically pure **(*R*)-15** {$[\alpha]_D^{20}$ = –37.99° (c = 0.90, MeOH)} (*Table 2*, entry 1). Optical purity (100% e.e.) of the latter was cross-checked by taking the ^{1}H NMR (500 MHz) spectrum of its (*R*)-(+)-MTPA ester [**(*R,R*)-17**] in C_6D_6. E.e. values for **15** shown in entries 3 and 4 were found by this method to be 64 and 35%, in excellent agreement with values calculated from optical rotations (65 and 36% respectively).

(*R*)-2-Phenoxypropyl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionate [(*R,R*)-17] (direct method). A mixture of (*R*)-(+)-3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid [(*R*)-(+)-MTPA, Mosher's acid, **(*R*)-16**] (345 mg, 1.47 mmol), Et_3N (0.7 mL, 5 mmol), CCl_4 (0.5 mL, 5 mmol), Ph_3P (0.62 g, 2 mmol) and THF (2.0 mL) was stirred at rt and under Ar for 1 h. To this mixture was added alcohol **(*R*)-15** (215 mg, 1.47 mmol) and stirring was continued for 24 h. Solvent and excess reagents were removed and the residue was triturated with hexane (15 mL). The mixture was stored for 2 h at rt and in a refrigerator overnight. The precipitated Ph_3PO was filtered off and washed with hexane (3x3 mL). The mother liquor and washings were combined, evaporated and the residue was purified by column chromatography on silica gel using 7% acetone in hexane as an eluent to give **(*R,R*)-17** (511 mg, 96%) as a clear oil. R_f = 0.34 (silica gel TLC, 10 % acetone in hexane); ^{1}H NMR (C_6D_6) δ 0.83 (d, J = 6 Hz, 3 H), 3.39 (s, 3 H), 3.83-3.86 (m, 1 H), 4.11-4.14 (m, 1 H), 4.24-4.28 (m, 1 H), 6.70 (d, J = 8 Hz, 2 H), 6.80 (t, J = 8 Hz, 1 H), 7.02-7.07 (m, 5H), 7.68 (d, J = 8 Hz, 2 H); ^{13}C NMR (C_6D_6) δ 16.40, 30.55, 55.75, 68.51, 71.51, 116.56, 121.85, 128.68, 128.96, 129.17, 130.07, 130.18, 133.24, 158.15, 166.87.

Mosher's esters of optically impure samples of alcohol **15** showed an extra doublet at δ = 0.89 (J = 6 Hz).

(2*S*,12*S*)-(-)-4,7,10-Trioxatridecane-2,12-diol di-*p*-tosylate [(*S,S*)-18]. Ditosylate **(*S,S*)-18** was prepared in the same way as described above for ditosylate **11** starting from (2*S*,12*S*)-(+)-4,7,10-trioxatridecane-2,12-diol **[(*S,S*)-20]**[44] (5.8 g, 0.026 mol). The crude product was purified by column chromatography on silica gel using 20% EtOAc in hexane as an eluent to give **(*S,S*)-18** (11.2 g, 81 %) as a clear oil. R_f = 0.32 (silica gel TLC, 25% EtOAc in hexane); $[\alpha]_D^{25}$ = –3.12° (c = 3.8, CH_2Cl_2); IR (neat) ν_{max} 3080, 3050, 3030, 2980, 2950, 2910, 2880, 2860, 1590, 1490, 1450, 1350, 1180, 1170, 1100, 1030, 910, 890, 810, 760, 660 cm^{-1}; ^{1}H NMR δ 1.26 (d, J = 6 Hz, 6 H), 2.44 (s, 6 H), 3.44-3.54 (m, 12 H), 4.68-4.71 (m, 2 H), 7.33 (d, J = 8 Hz, 4 H), 7.80 (d, J = 8 Hz, 4 H); ^{13}C NMR δ 17.47, 21.52, 70.36, 70.69, 73.28, 78.01, 127.71, 129.60, 134.13, 144.44. Anal. Calcd. for $C_{24}H_{34}O_9S_2$: C, 54.32; H, 6.46; S, 12.08. Found: C, 54.24; H, 6.45; S, 12.05.

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