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Synthesis and crystal structure of (+)-(2*R*,3*R*)-*N*, *N*′-bis-trityl-2,3-bis-aziridine

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A new C_2 symmetric bis-aziridine derivative was synthesized starting from *L*-(+)-tartaric acid. The molecular structure of (+)-(2*R*, 3*R*)-*N*, *N*′-bis-trityl-2,3-bis-aziridine **4,** was determined by ^1H, ^{13}C NMR and elemental analysis and was confirmed by single-crystal X-ray diffraction. Crystal data for **4:** $C_{42}H_{36}N_2$, orthorhombic, space group: $P2_12_12_1$, a = 12.7633(14), b = 14.5661(6), c = 17.4184(14) Å, and Z = 4.

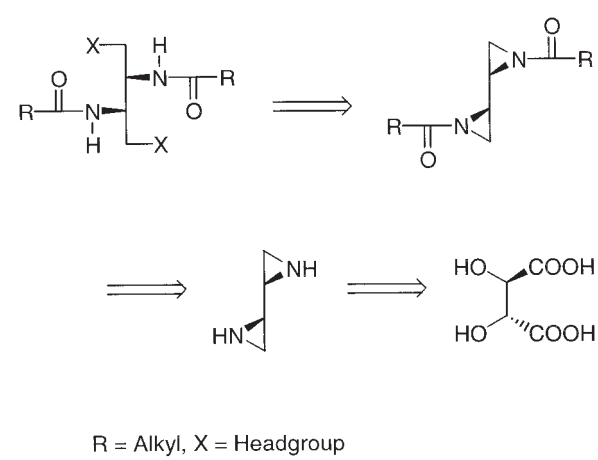
KEY WORDS: Bis-aziridine; C_2-symmetric compound; *L*-(+)-tartaric acid.

Introduction

Aziridine rings are present in many synthetic and natural compounds of biological importance.[1] They have been used in the synthesis of β-lactam antibiotics,[2] amino sugar derivatives,[3] and surfactants.[4] In this respect chiral aziridines form an interesting class of compounds, since they are available in enantiopure form starting from simple materials by various routes.[1,5]

Enantiopure surfactants can assemble to form chiral supramolecular structures. The expression of molecular chirality on a supramolecular level requires a high degree of organization within the aggregates. In particular, the formation of a hydrogen bonding network of secondary amides has been effectively used[6] to achieve this organization. Currently, the synthesis and aggregation behavior of dimeric or so-called gemini surfactants is receiving much attention.[7] Therefore, it would be of interest to synthesize chiral gemini surfactants containing secondary amides using the synthetic methodology developed in our laboratory.[4] This would require the development of a bis-aziridine building block starting from tartaric acid (Scheme 1).

Through known literature procedures, this compound can easily be converted into a bis-aziridine compound. Acylation of this compound with a suitable fatty acid followed by ring opening would result in amide containing gemini surfactants as depicted in Scheme 1 in a retrosynthetic manner.



Scheme 1. Retrosynthetic scheme of the synthesis of amide containing gemini surfactants.

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Experimental section

General remarks

Optical rotations were determined with a Perkin-Elmer automatic polarimeter, model 241 MC using 1% solutions at 20°C in the solvents indicated. Melting points were determined using a Reichert thermopan microscope equipped with crossed polarizers, and are uncorrected. ^{1}H NMR experiments were performed on a Bruker AC 100 (100 MHz, FT or a Bruker AC 400 (400 MHz, FT) spectrometer using solutions in $CDCl_3$ (internal standard Me_4Si). Routine FT-IR spectra were recorded on a Biorad WIN-IR FTS-25 spectrometer. Elemental analyses were performed on a Carlo Erba CHNS-O EA 1108 element analyzer. Mass spectra were obtained with a double focusing VG 7070E spectrometer. Diethyl ether was pre-dried over potassium hydroxide, then distilled from sodium/benzophenone. Dimethyl formamide was dried by stirring overnight with BaO followed by distillation under vacuum. Thin-layer chromatography was carried out on Merck precoated silica gel 60 F254 plates (0.25 mm) using the eluents indicated. Spots were visualized with UV or using molybdate spray. Flash column chromatography was carried out at a pressure of ca. 1.0 bar, using Merck Kieselgel 60H.

Table 1. Crystal Data and Refinement for Compound 4

Empirical formula	$C_{42}H_{36}N_2$
CCDC deposit no.	CCDC-1003/5488
Color/shape	colorless transparent/regular
Formula weight	568.73
Temperature	293(2) K
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	a = 12.7633(14) Å
(25 reflections	b = 14.5661(6) Å
$20.481 < \theta < 23.068$)	c = 17.4184(14) Å
Volume	3238.3(5) Å^3
Z, Calculated density	4, 1.167 mg/m^3
Absorption coefficient	0.512 mm^{-1}
Diffractometer/scan	Enraf-Nonius CAD4/θ-2θ
Radiation/wavelength	CuK_α (graphite monochrom./ 1.54184 Å)
F(000)	1208
Crystal size	0.29 × 0.17 × 0.09 mm
θ range for data collection	3.96 to 69.93°
Index ranges	$-15 \le h \le 0$, $-17 \le k \le 0$, $-21 \le l \le 0$
Reflections collected	3449
Independent/observed refls.	3449(R_{int} = 0.0000)/2473([$I_o > 2\sigma(I_o)$])
Absorption correction	Semi-empirical from ψ[13]
Range of relat. transm. factors	0.906 and 1.124
Refinement method	Full-matrix, least-squares on F^2
Computing	SHELXL-93[9]
Data/restraints/parameters	3449/0/542
Goodness-of-fit on F^2	1.077
SHELXL-93 weight parameters	0.0679 and 0.4404
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0535, wR_2 = 0.1224
R indices (all data)	R_1 = 0.0828, wR_2 = 0.1394
Extinction coefficient	0.0017(2)
Largest diff. peak and hole	0.197 and −0.164 e. Å^{-3}

Synthesis

(−)-(2S, 3S)-1,4-Diazido-2,3-butanediol (2). Sodium azide (7.0 g, 107 mmol) was added to a solution of (2*S,* 3*S*)-1,4-*O*-ditosyl threitol[7e] **1** (11.4 g, 26.5 mmol) in DMF (170 ml) and the mixture was heated for 2 h at 80°C. After cooling, water (150 ml) was added and the reaction mixture was extracted with diethyl ether (3 × 50 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo.* The crude product was purified by flash column chromatography (SiO_2, ethyl acetate-hexane, 1:1 (v/v)) to give a colorless oil in 59% yield. R_f = 0.53 (SiO_2, ethyl acetate-hexane, 1:1 (v/v)); $[\alpha]^{20}_D$ −13.0 (c 1.00, $CHCl_3$); IR (KBr, cm^{-1}): 3391 (OH), 2931 (CH), 2105 (N_3); ^{1}H-NMR ($CDCl_3$, 100 MHz, ppm): δ 2.4 (d, 2H, J = 4.9 Hz, 2 × O*H*), 3.4 (d, 4H, J = 6.5 Hz, 2 × CH_2N_3), 3.7 (m, 2H, 2 × C*H*OH); MS (EI, *m/z,* rel. int. (%)): 172 (M^+, 4.4), 155 ($C_4H_7N_6O^+$, 4.3), 116 ($C_3H_6N_3O_2^+$, 24.0), 42 (N_3^+, 54.8), 28 (N_2^+, 100).

(+)-(2R, 3R)-N, N′-bis-trityl-2,3-bis-aziridine (4). To a solution of **2** (100 mg, 0.58 mmol) in dry acetonitrile triphenylphosphine (300 mg, 1.14 mmol) was added and the mixture was stirred at room temperature for 18 h. Subsequently, the reaction mixture was heated under reflux for 4 h and concentrated *in vacuo.* The crude reaction mixture was dissolved in CH_2Cl_2 (10 ml) and cooled to −18°C. To the cooled solution, pyridine (0.4 ml) and trityl chloride (350 mg, 1.28 mmol) were added and the mixture was kept at −18°C for 1 h. Hereafter the reaction mixture was allowed to warm to room temperature and stirred for 1 h. After washing with citric acid (10% (w/w) 2 × 10 ml) and saturated Na_2CO_3 (10 ml), the reaction mixture was dried (Na_2SO_4) and concentrated. The crude mixture was purified with flash chromatography (SiO_2, ethyl acetate–hexane, 1:12 (v/v)) to afford

a colorless solid in 15% overall yield. The compound could be crystallized by adding **4** dissolved in $CHCl_3$ (1.5 ml) with the help of a Pasteur pipette to the bottom of a test tube which contained MeOH (0.5 ml). After 1 week colorless crystals were obtained which were suitable for x-ray analysis. $R_f = 0.56$ (SiO_2, ethyl acetate-hexane, 1:12 (v/v)); $[\alpha]^{20}D^+$ 156.5 (c 1.00, $CHCl_3$); IR (KBr, cm^{-1}) 3100–3000 (C—H, aryl),* 3000–2900 (C—H, alkyl); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.42–7.08 (m, 30H, 2 × $C_{19}H_{15}$), 1.62-1.61 (m, 2H, 2 × C*H*H), 1.50–1.45 (m, 2H, 2 × C*H*), 1.06–1.05 (m, 2H, 2 × CH*H*); ^{13}C-NMR ($CDCl_3$, 35 MHz): δ 25.0 (*C*H_2), 33.7 (*C*H), 74.0 (*C*(C_6H_5)$_3$), 126.6 (*p*-C(*C*$_6$H$_5$)$_3$), 127.3 (*o*-C(*C*$_6$H$_5$)$_3$), 129.5 (*m*-C(*C*$_6$H$_5$)$_3$), 144.5 (*C* q, arom); MS (FAB$^+$, *m/z*): 568 (M^+), 325 ($C_{23}H_{21}N_2^+$), 243 ($C_{19}H_{15}^+$). Analysis calcd. for $C_{42}H_{36}N_2$: C, 88.70; H, 6.38; N, 4.93. Found: C, 88.89; H, 6.23; N, 5.23.

Table 2. Atomic Coordinates (× 10^4) and Equivalent Isotropic Displacement Parameters (Å^2 × 10^3) for **4**

	x/a	y/b	z/c	*U*(eq)
N(1)	−4018(2)	−2387(2)	−2255(2)	45(1)
C(1)	−3121(3)	−2628(3)	−1744(2)	42(1)
C(2	−4535(5	−1510(4)	−2175(4)	78(2)
C(3)	−3928(4)	−1724(3)	−2867(3)	58(1)
C(10)	−2711(3)	−3570(3)	−2008(2)	43(1)
C(11)	−3265(3)	−4105(3)	−2525(2)	51(1)
C(12)	−2927(4)	−4986(3)	−2706(3)	63(1)
C(13)	−2027(4)	−5342(3)	−2381(3)	64(1)
C(14)	−1470(4)	−4816(3)	−1873(3)	64(1)
C(15)	−1795(4)	−3946(3)	−1689(2)	56(1)
C(20)	−3551(3)	−2779(3)	−933(2)	49(1)
C(21)	−4613(4)	−3004(4)	−828(3)	72(1)
C(22)	−4983(6)	−3197(5)	−106(4)	90(2)
C(23)	−4357(6)	−3159(4)	518(4)	90(2)
C(24)	−3300(6)	−2965(4)	432(3)	78(2)
C(25)	−2916(4)	−2774(3)	−296(2)	58(1)
C(30)	−2261(3)	−1890(3)	−1784(2)	42(1)
C(31)	−2288(3)	−1115(3)	−1321(2)	49(1)
C(32)	1595(4)	−398(3)	−1414(3)	62(1)
C(33)	−842(4)	−441(3)	−1985(3)	64(1)
C(34)	−802(3)	−1197(3)	−2454(3)	60(1)
C(35)	−1498(3)	−1924(3)	−2352(2)	49(1)
N(1′)	−4916(2)	−2805(2)	−3753(2)	46(1)
C(1′)	−5955(3)	−2885(3)	−4151(2)	43(1)
C(2′)	−3991(4)	−2550(5)	−4199(3)	75(2)
C(3′)	−4435(3)	−1913(3)	−3624(3)	59(1)
C(10′)	−6771(3)	−2989(3)	−3504(2)	43(1)
C(11′)	−6502(4)	−3277(4)	−2778(2)	61(1)
C(12′)	−7253(4)	−3384(4)	−2212(3)	79(2)
C(13′)	−8293(4)	−3212(4)	−2366(3)	71(2)
C(14′)	−8572(4)	−2932(4)	−3078(3)	62(1)
C(15′)	−7840(3)	−2817(3)	−3653(3)	56(1)
C(20′)	−5928(3)	−3807(3)	−4586(2)	47(1)
C(21′)	−5131(5)	−4447(4)	−4481(3)	71(1)
C(22′)	−5145(7)	−5274(4)	−4881(4)	94(2)
C(23′)	−5915(7)	−5477(4)	−5384(4)	93(2)
C(24′)	−6714(6)	−4858(4)	−5489(3)	83(2)
C(25′)	−6726(5)	−4031(3)	−5092(3)	63(1)
C(30′)	−6188(3)	−2072(3)	−4673(2)	42(1)
C(31′)	−5933(3)	−2074(3)	−5445(2)	47(1)
C(32′)	−6086(4)	−1301(3)	−5898(2)	59(1)
C(33′)	−6477(4)	−512(3)	−5578(3)	66(1)
C(34′)	−6718(4)	−487(3)	−4813(3)	63(1)
C(35′)	−6581(3)	−1257(3)	−4365(2)	51(1)

[a] *U*(eq) is defined as one-third of the trace of the orthogonalized U_{ij} tensor.

X-ray data collection, structure solution and refinement

Crystals of **4** suitable for X-ray diffraction studies were obtained by recrystallization from methanol and chloroform via slow diffusion. A single crystal was mounted on a glass fiber. Intensity data were collected at room temperature and were corrected for Lorentz and polarization effects. The crystal structure was determined using the program CRUNCH.[8] The structure was refined by full-matrix least squares on F^2 values using SHELXL[9] with anisotropic parameters for the non-hydrogen atoms. All hydrogen atoms were initially placed at the calculated positions and were freely refined subsequently. The plots of the molecule were made with PLATON.[10] Table 1 summarizes the crystal data, data collection, and structure refinement for **4,** and the atomic coordinates of the compound are given in Table 2. The structure and atomic numbering are presented in Fig. 1.

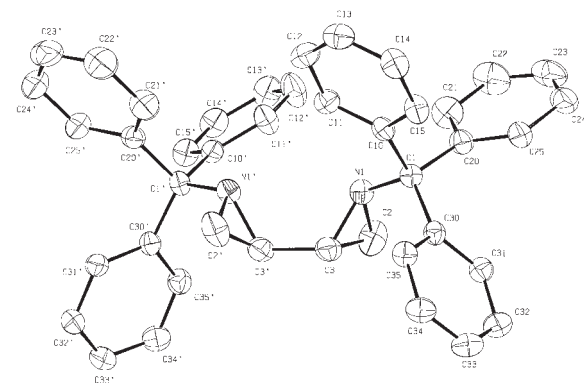


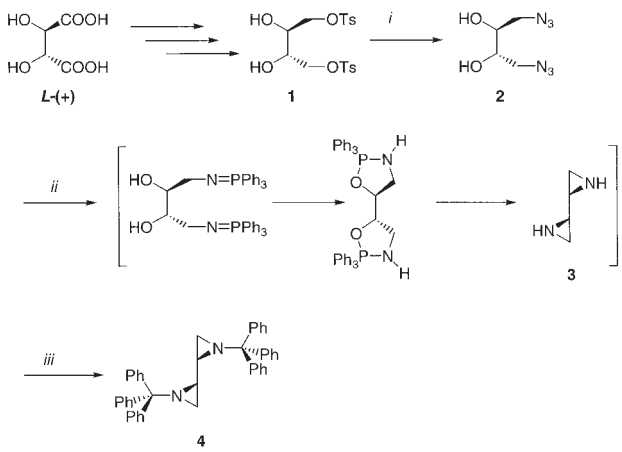
Fig. 1. ORTEP representation of the crystal structure of **4.** Thermal ellipsoids are at 40% probability.

Results and discussion

The optically active bistosylate **1** (Scheme 2) was obtained from *L*-(+)-tartaric acid using literature procedures.[11] The conversion of **1** into the corresponding diazido butane diol **2** using sodium azide in DMF at 80°C proceeded smoothly in moderate yield. The diazido diol was transformed into the bis-aziridine by reaction with triphenylphosphine. In this, a so-called Staudinger reaction,[12] azido alcohol **2** reacts with triphenylphosphine under concomitant extrusion of nitrogen to form a phosphazo compound. Intramolecular addition of the hydroxyl functions leads to the formation of oxazaphospholidines, which upon cleavage of the P—N bond, undergo an intramolecular substitution reaction with elimination of triphenylphosphine oxide, to give the bis-aziridine **3** (Scheme 2).

The isolation of this compound was rather cumbersome. Distillation and column chromatography were not successful. Extraction of the crude reaction mixture with diethyl ether, washing the extract with water, and subsequent lyophilization afforded a colorless oil. Mass spectrometry revealed the molecular ion peak (84, M^+) but other spectral data (^{1}H NMR, IR) were not conclusive.

Establishment of the bis-aziridine structure was therefore performed by derivatization. For this purpose, **3** was converted to the N-trityl derivative **4** by treatment of the crude reaction mixture with trityl chloride and base in dichloromethane. After column chromatography and crystallization from chloroform and methanol, crystals were obtained which were suitable for X-ray analysis.



Scheme 2. The synthesis of (+)-(2*R,* 3*R*)-*N, N′*-bis-trityl-2,3-bis-aziridine, **4**.

Table 3. Selected Dihedral Angles [°] for 4

	Dihedral angle (°)
N(1)—C(1)—C(10)—C(11)	−11.13(45)
N(1)—C(1)—C(20)—C(21)	22.51(56)
N(1)—C(1)—C(30)—C(31)	86.44(41)
N(1′)—C(1′)—C(10′)—C(11′)	−20.54(51)
N(1′)—C(1′)—C(20′)—C(21′)	9.38(50)
N(1′)—C(1′)—C(30′)—C(31′)	92.52(42)
C(2)—N(1)—C(1)—C(10)	−176.61(40)
C(2′)—N(1′)—C(1′)—C(10′)	−170.19(43)

The molecule possesses a slightly distorted C_2-symmetry, as can be deduced from the selected dihedral angles listed in Table 3, which correspond to the free rotable bonds in the molecule.

The results presented show unambiguously that a new enantiopure bis-aziridine derivative has been synthesized starting from tartaric acid. Removal of the trityl groups allows functionalization of the aziridine rings and the introduction of, for instance, long alkyl chains in order to synthesize new gemini surfactants. Studies along this line are underway.

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