(20 mL) was added a solution of **19a** (317 mg, 1 mmol) (or 331 mg, 1 mmol of **19b**) in THF (10 mL) under ice cooling. After the stirring had been continued for 6 h at room temperature, the mixture was decomposed with 20% NaOH. The inorganic precipitate was filtered off, and the filtrate was evaporated to give **20a** (208 mg, 85%): mp 69–71 °C (ether–hexane) (lit.[16] oil); ^{1}H NMR ($CDCl_3$) δ 7.56–7.12 (5 H, m), 4.09–3.72 (1 H, m), 2.08 (3 H, s); IR ($CHCl_3$) 3650, 3590, 1600, 1500, 1470 cm^{-1}; MS, m/z 245 (M^+). Anal. Calcd for $C_{16}H_{23}NO\ H_2O$: C, 72.96; H, 9.57; N, 5.32. Found: C, 72.95; H, 9.41; N, 5.24.

Synthesis of 22. To a sitrred solution of **19b** (800 mg, 2.4 mmol) in EtOH (10 mL) was added 3 N NaOH (1 mL) under ice cooling. The mixture was kept at room temperature under stirring for 0.5 h, poured into saturated Na_2CO_3, and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and evaporated to give **22** (690 mg, 95%) as an oil; this was used for the following reaction without purification. MS, m/z 303 (M^+); IR ($CHCl_3$) 3600, 3400 (OH), 1680 (C=O) cm^{-1}.

The Xanthate 23. To a stirred solution of **22** (150 mg, 0.495 mmol) in THF (5 mL) was added NaH (99 mg of 60% mineral oil dipersion, 2.475 mmol) and a pinch of imidazole. After the mixture was warmed at 65 °C for 10 min, carbon disulfide (0.17 mL, 2.97 mmol) was added to the reaction mixture. The mixture was kept at 65 °C under stirring, and idomethane (0.18 mL, 2.97 mmol) was added. After the stirring had been continued at the same temperature for 40 min, the mixture was poured into saturated NaCl and extracted with CH_2Cl_2–ether (1:2). The extract was washed with brine, dried (Na_2SO_4), and evaporated. The resulting residue was chromatographed on silica gel (7 g). Elution with hexane–ether (5:1) gave **23** (118 mg, 60%) as an oil: ^{1}H NMR ($CDCl_3$) (as characteristic signal) δ 7.57–7.07 (5 H, m), 6.00–5.57 (1 H, m), 4.08 (2 H, q, J = 7 Hz), 2.99 (1 H, d, d, J = 14 and 2 Hz), 2.77 (1 H, d with small splitting, J = 14 Hz), 2.42 (3 H, s), 1.22 (3 H, t, J = 7 Hz); IR ($CHCl_3$) 1690 (C=O) cm^{-1}; MS, m/z 393 (M^+, 5%), 348 (50%), 286 (100%).

Synthesis of 24. A mixture of **23** (410 mg, 1.04 mmol), tri-*n*-butyltin hydride (1.95 mL, 2.6 mmol), a pinch of 2,2′-azobis(2-methylpropionitrile), and benzene (26 mL) was heated under reflux for 0.5 h. The solvent was evaporated and the remaining residue was chromatographed on silica gel (15 g). Elution with hexane–ether (5:1) gave **24** (180 mg, 60%) as an oil: ^{1}H NMR ($CDCl_3$) (as characteristic signal) δ 7.50–7.03 (5 H, m), 4.09 (2 H, q, J = 7 Hz), 3.59 (1 H, d, d, J = 13 and 5 Hz), 3.20 (1 H, d, d, J = 13 and 3 Hz), 1.22 (3 H, t, J = 7 Hz); IR ($CHCl_3$) 1680 (C=O) cm^{-1}; MS, m/z 287 (M^+), exact mass, m/z 287.1887 (calcd for $C_{18}H_{25}NO_2$, m/z 287.1884).

***cis*-2-Methyl-4a-phenyldecahydroisoquinoline (25).** To a stirred solution of **24** (182 mg, 0.63 mmol) in THF (6.3 mL) was added $LiAlH_4$ (2.2 mL of 1 M solution in THF) under ice cooling. The mixture was allowed to stand at room temperature for 12 h and then decomposed with 20% NaOH. Inorganic precipitate was filtered off, and the filtrate was evaporated to give **25** (122 mg, 84.5%) as an oil: ^{1}H NMR ($CDCl_3$) (as characteristic signal) δ 7.53–7.00 (5 H, m), 2.22 (3 H, s); MS, m/z 229 (M^+). Picrate mp 153–156 °C (lit.[2,16] 144–146 °C). Anal. Calcd for $C_{22}H_{25}N_4O_7$: C, 57.63; H, 5.72; N, 12.22. Found: C, 57.83; H, 5.81; N, 12.22. Hydrochloride mp 219–221 °C (MeOH–ether) (lit.[4] 219.5–221.5 °C). Anal. Calcd for $C_{16}H_{23}N$ HCl: C, 72.29; H, 9.10; N, 5.27. Found: C, 71.97; H, 8.85; N, 5.18.

Preparation of 26. A mixture of **13b** (273 mg, 1.0 mmol) (or 273 mg, 1.0 mmol of **18b**), paraformaldehyde (30 mg, 1 mmol), and sodium formate (68 mg, 1.0 mmol) and formic acid (1 mL) was stirred for 3 h at room temperature. The mixture was worked up as above to yield **26** (291 mg, 88%): ^{1}H NMR ($CDCl_3$) δ 8.29 (0.2 H, OCHO), 7.98 (0.8 H, OCHO), 5.78–5.24 (1 H, m), 5.04–4.64 (2 H, m); IR ($CHCl_3$) 1730, 1700, 1645 cm^{-1}; MS, m/z 331 (M^+).

Cyclization of 26. A mixture of **26** (248 mg, 0.75 mmol) and formic acid (1 mL) was stirred for 1.5 h at room temperature and worked up as above to give **19b** (236 mg, 95%), which was identical with that obtained from **13b** and **18b**.

Synthesis of 27. To a stirred solution of **2** (200 mg, 0.66 mmol) in acetone (5 mL) was added Jones reagent (1.3 mmol, 1.9 mL of 0.7 M solution prepared from 70 g of CrO_3, 61 mL of concentrated H_2SO_4, and water) under ice cooling. After 10 min, the mixture was diluted with water and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and evaporated to give **27** (167 mg, 85%): mp 99–100 °C; ^{1}H NMR ($CDCl_3$) δ 7.49–7.02 (5 H, m, ArH), 4.09 (2 H, q, J = 7 Hz, OCH_2CH_3), 3.70–3.39 (4 H, m, CH_2NCH_2), 2.60 (2 H, s, 5-H_2), 1.24 (3 H, t, J = 7 Hz, OCH_2CH_3); IR ($CHCl_3$) 1705 (C=O), 1690 (NCO) cm^{-1}; MS, m/z 301 (M^+). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.97; H, 7.73; N, 4.69.

Synthesis of 20b. To a stirred suspension of $LiAlH_4$ (100 mg, 0.4 mmol) in THF (5 mL) was added a solution of **27** (119 mg, 0.4 mmol) in THF (5 mL) under ice cooling. After the sitrring had been continued at room temperature for 12 h, the mixture was worked up as usual to give **20b** as an oil contaminated with a small quantity of **20a** (80 mg, 81%). ^{1}H NMR ($CDCl_3$) δ 7.55–7.05 (5 H, m, ArH), 3.81–3.38 (1 H, m, $W_{1/2}$ = 21 Hz, 6-H), 2.29 (3 H, s, NCH_3); IR ($CHCl_3$) 3640, 3580, 3300, 1600, 1500, 1480, 690 cm^{-1}; MS, m/z 245 (M^+) picrate, mp 104–106 °C (EtOH). Anal. Calcd for $C_{22}H_{26}N_4O_8 \cdot 0.5\ H_2O$): C, 54.65; H, 5.63; N, 11.59. Found: C, 54.50; H, 5.78; N, 10.98.

Registry No. **6**, 17605-06-0; **7**, 97523-07-4; **8**, 97523-08-5; **9**, 97523-09-6; **10**, 97523-10-9; **11**, 97523-11-0; **13a**, 97523-12-1; **13b**, 97523-13-2; **14**, 87046-18-2; **16**, 87046-20-6; **17**, 87046-21-7; **18a**, 97523-14-3; **18b**, 87046-26-2; **19a**, 97523-15-4; **19b**, 97523-16-5; **20a**, 50640-76-1; **20b**, 50640-77-2; **22**, 97523-17-6; **23**, 97523-18-7; **24**, 97523-19-8; **25**, 50640-86-3; *cis*-**26**, 97523-20-1; *trans*-**26**, 97523-22-3; **27**, 97523-21-2; PhC(Br)=CH_2, 98-81-7; CH_2=$CH(CH_2)_2CHO$, 2100-17-6.

Synthesis of $[H^+\subset(1.1.1)]X^-$ Cryptates Assisted by Intramolecular Hydrogen Bonding[1]

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Condensation of [1.1] diazacoronand and diethylene glycol bis(methanesulfonate) as well as with its alkyl-substituted derivatives in the presence of 1 molar equiv of BuLi or KH gives the corresponding $[H^+\subset(1.1.1)]X^-$ cryptates in 31–43% yields. Experimental results indicate that in the intermediate monosubstituted diazacoronand, the NH hydrogen plays a templating role, thus favoring the bicyclic ring closure by intramolecular hydrogen bonding. Similar base-promoted condensations of [2.1] and [2.2] diazacoronands with triethylene glycol bis(methanesulfonates) afford [2.2.1] and [2.2.2] cryptates in 20–35% yields.

Parameters ruling selectivity of complexation of cryptands with metal cations and the stability of the resulting cryptates are well documented.[2] The [1.1.1] cryptand **1** is capable of selectively binding one or two protons inside

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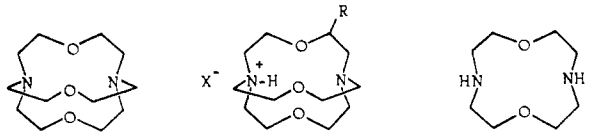

1 2, R = H 3, R = $C_{14}H_{29}$-*n* 4

its intramolecular cavity.[3] This cryptand is of exceptional interest because the trapped proton of the monoprotonated species **2** does not undergo any intermolecular exchange and cannot be removed.[3] When cryptates are made soluble in low-polarity media by introduction of a long alkyl chain, a very high anionic activation is observed due to the poor anion solvation and the large interionic separation imposed by the topology of the system.[4] We were interested in the synthesis of $[H^+\subset(1.1.1,C_{14})]X^-$ cryptates **3** in order to extend a series of investigations on the reactivity of anions in nonpolar media.[5,6] Unfortunately the synthesis reported for **1** gives very low yields, the main reaction product being a cylindrane in which two diazacoronand rings are connected by two diethyleneoxy bridges.[3] We therefore took a completely different approach, which directly gave proton cryptates **2** and **3** in satisfactory yields.

α-Bromopalmitic acid was reacted with ethylene glycol monobenzyl ether to give first the ester **5** and then the ether **6** (Scheme I).[7] Alkaline hydrolysis of **6** and hydrogenolysis of **7** (Pd/C, ethanol) afforded lactone **8**. Alternatively, **8** was obtained by hydrogenolysis of **5** to bromo ester **9** and cyclization of the latter via sodium or potassium salt. Reduction of **8** with $LiAlH_4$ in THF afforded tetradecyldiethyleneglycol **10**, which was converted into the corresponding bis(methanesulfonate) **11** and dichloride **12**.

Diazacoronand **4** was obtained, as described,[3] from diglycolic acid dichloride and 2,2′-diaminodiethyl ether **16**. The latter, which is extremely hygroscopic and is extracted with difficulty from aqueous solutions,[3] was synthetized in high yields by catalytic hydrogenation of diazide **15**, which was obtained from dichloro ether **14** under phase-transfer conditions.

The monolithium derivative of diazacoronand **4** (from **4** and 1 molar equiv of BuLi in THF) was finally condensed with bis(methanesulfonate) **11** (4 days in boiling THF) to afford cryptate **3**, isolated as iodide (X = I) in 43% yield (Table I), after anionic exchange and column chromatography.

Structure **3** unambiguously results from analytical and ^1H NMR data. A broad singlet at δ 8.8 in $CDCl_3$ (δ 9.6 in D_2O) indicates the presence of an N^+H hydrogen inside the bicyclic system. This hydrogen does not exchange with deuterium in D_2O solution, in agreement with the behavior of the unsubstituted monoproton cryptate **2**.[3]

Similar results were obtained when the reaction between **4** and **11** was repeated with 1 molar equiv of KH instead of BuLi. Yields were lower by using the dichloro derivative **12** instead of **11**. When 2 molar equiv of base (BuLi or KH) were used no cryptate **3** was obtained, but only unresolvable mixtures of open chain polymeric materials were obtained.

From diethylene glycol bis(methanesulfonate) **13** and diazacoronand **4** in the presence of 1 molar equiv of BuLi or KH, the unsubstituted [1.1.1] macrobicyclic system was obtained, again as the proton cryptate **2**, which directly

Scheme I

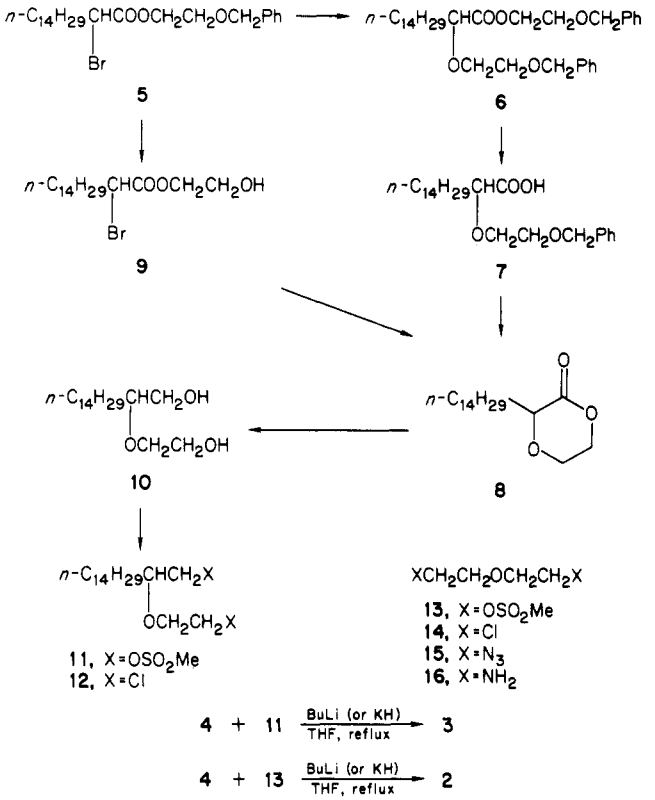

Table I. Base-Promoted Condensations of Diazacoronands with Di- and Triethylene Glycol Bis(methanesulfonates)

entry	diazacoronand	bis(methanesulfonate)	base[a]	product	yield, %
1	[1.1]	**13**	BuLi(1)	[1.1.1]	40[b]
2	[1.1]	**13**	KH (1)	[1.1.1]	40[b]
3	[1.1]	**11**	BuLi (1)	[1.1.1,C_{14}]	43[c,d]
4	[1.1]	**11**	KH (1)	[1.1.1,C_{14}]	31[c]
5	[1.1]	**11**	Na_2CO_3 (3)	[1.1.1,C_{14}]	21[c]
6	[2.1]	**17**	Li_2CO_3 (3)	[2.2.1]	26[e]
7	[2.1]	**17**	Na_2CO_3 (3)	[2.2.1]	28[f]
8	[2.1]	**17**	K_2CO_3 (3)	[2.2.1]	17[g]
9	[2.1]	**18**	NaH (1) Na_2CO_3 (3)	[2.2.1,C_{14}]	35[f]
10	[2.2]	**17**	BuLi (1)	[2.2.2]	25[g]
11	[2.2]	**17**	NaH (1)	[2.2.2]	22[f]
12	[2.2]	**17**	Na_2CO_3 (1)	[2.2.2]	20.5[f]
13	[2.2]	**18**	BuLi (1)	[2.2.2,C_{14}]	26[h]

[a] Molar equivalents in parenthesis. [b] Isolated as $(H^+\subset 2)$-$MeSO_3^-$. [c] Isolated as $(H^+\subset 3)I^-$. [d] Using **12** instead of **11**, yield was 29%. [e] Isolated as LiI cryptate. [f] Isolated as NaI cryptate. [g] Isolated as KI cryptate. [h] Isolated as cryptand.

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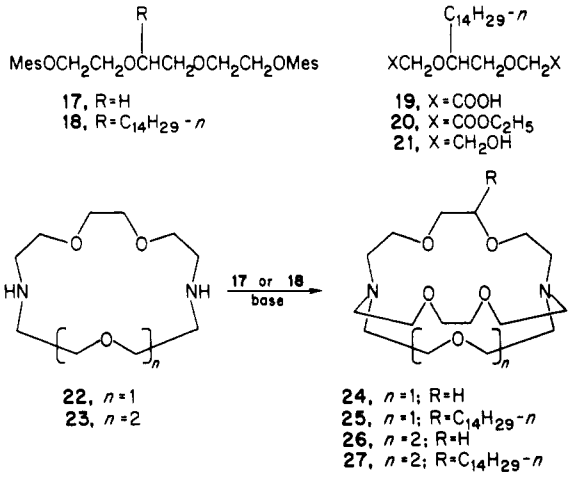
(7) The use of ethyl or *tert*-butyl α-bromopalmitates instead of **5** afforded poor results due to competitive transesterifications.

Scheme II



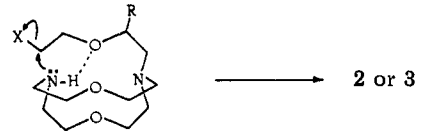
precipitates as mesylate (X = OSO_2Me) from the boiling THF solution in 40% yield.

In order to study the extension of this reaction to the synthesis of other cryptands, [2.1] and [2.2] diazacoronands **22** and **23** were condensed with triethylene glycol bis(methanesulfonate) **17** and with its tetradecyl derivative **18** (Scheme II). The latter was easily prepared from bicarboxylic acid **19**,[8] via diester **20** and diol **21**.

Working under conditions similar to those followed for the synthesis of [1.1.1] cryptates, [2.2.1] cryptates **24** and **25** and [2.2.2] cryptates **26** and **27** were isolated, respectively, in 20–35% yields (Table I).

Similar yields were obtained in the presence of a slight excess (3 molar equiv) of alkaline carbonates, whereas use of the latter afforded noticeably lower yields in the synthesis of [1.1.1] cryptates.

The experimental results indicate that, at least for [1.1.1] cryptates, the reaction should proceed through the monosubstituted diazacoronand **28**, in its turn formed by the reaction of monometalated **4** with **11** or **13** or by quaternarization of nitrogen in **4** and deprotonation to **28** when alkali carbonates are used. In the intermediate **28** the NH

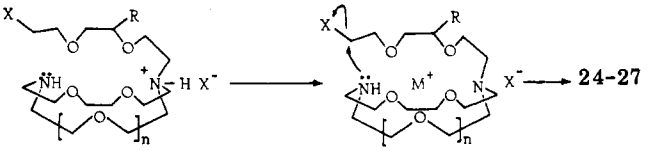


28, R = H, $C_{14}H_{29}$-*n*

hydrogen can play a templating role by intramolecular hydrogen bonding with the ethereal oxygen of the incoming chain thus leading to the bicyclic ring closure. This conclusion rests on the following: (i) only one molecule of BuLi or KH is required, whereas bis metalation of diazacoronand **4** leads to polymeric materials; (ii) yields are independent of the metal cation (Li^+ or K^+); (iii) the NH proton is irreversibly trapped inside the bicyclic system; it is worth noting that cryptate **2** is isolated by filtration from the reaction mixture in the absence of any external source of protons.

A similar intervention of intramolecular hydrogen bonding in the synthesis of N_4 macrocyclic imine ligands has been reported.[9]

It cannot be excluded that also for [2.2.1] and [2.2.2] cryptates the closure of the bicyclic ring is favored by intramolecular hydrogen bonding. It is more likely that



a templating effect of a metal cation is involved, since both alkali cations can be included and protons removed easily from the intramolecular cavities of [2.2.1] and [2.2.2] systems.

Indeed, base-promoted condensations of diazacoronands **22** and **23** with phenanthroline and bipyridine moieties to afford rigid [2.2.2] cryptates is allowed by the templating effect of Na^+ cation.[10] The one-pot Na^+ template synthesis of [2.2.2] cryptate from the chloro–iodo derivative of triethylene glycol and the corresponding diamine has also been described.[11]

In conclusion, the synthetic route here reported represents a new approach to the synthesis of cryptates: proton cryptates **2** and **3** are obtained from diazacrown **4** in a single step, avoiding the high-dilution technique and the three steps otherwise required.[3] Due to its simplicity and despite its modest yields, it also offers an alternative to the classical synthesis of larger cryptates via bicyclic diamides.

Experimental Section

^1H NMR spectra were recorded at 90 MHz on a Varian EM-390 or at 200 MHz on a Varian XL 200 spectrometer with Me_4Si as an internal standard. Infrared spectra were obtained with a Perkin-Elmer 377 spectrometer. Potentiometric titrations were performed with a Metrohm Titroprocessor E 636 and Metrohm Dosimat E 635. Melting points were measured on a Buchi 510 apparatus and are uncorrected. Satisfactory combustion analyses were obtained (C, ±0.40; H, ±0.20; N, ±0.40) for all new compounds. Organic and inorganic reagents, ACS grade, were used without further purification. α-Bromopalmitic acid,[12] 1,7-dioxa-4,10-diazacyclododecane,[3] 4-tetradecyl-3,6-dioxaoctane-1,8-dicarboxylic acid,[8] 2-(benzyloxy)ethanol,[13] and diethylene glycol dimethanesulfonate[14] were prepared according to known procedures.

2-(Benzyloxy)ethyl 2-Bromohexadecanoate (5). A solution of 14.12 g (0.04 mol) of 2-bromopalmitoyl chloride in 30 mL of anhydrous benzene was dripped into a magnetically stirred solution of 6.08 g (0.044 mol) of 2-(benzyloxy)ethanol and 6.32 g (0.08 mol) of anhydrous pyridine in 30 mL of benzene. The mixture was refluxed for 2.5 h. After cooling at room temperature and addition of 100 mL of H_2O, the mixture was transferred into a separatory funnel. The organic phase was diluted with ethyl ether, washed with aqueous 1 M H_2SO_4 and with brine, and dried with $MgSO_4$ and the solvent evaporated to give 18.0 g of a crude oily product. Column chromatography (silica gel, ethyl ether–light petroleum) afforded 14.4 g (80%) of **5** as an oil: n^{20}_D 1.4910; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.05–1.60 (m, 24 H), 1.75–2.15 (m, 2 H), 3.65 (t, 2 H), 4.10–4.40 (m, 3 H), 4.50 (s, 2 H), 7.25 (s, 5 H).

2-(Benzyloxy)ethyl 2-[2-(Benzyloxy)ethoxy]hexadecanoate (6). Potassium metal (1.17 g, 0.03 mol) was added to a solution of 4.57 g (0.03 mol) of 2-(benzyloxy)ethanol in 30 mL of anhydrous toluene, and the stirred mixture was heated at 90 °C until the potassium was completely dissolved. A solution of 9.4 g (0.02 mol) of **5** in 20 mL of toluene was added; stirring and heating were maintained for 15 h. The reaction mixture was acidified with aqueous 1 M H_2SO_4 and extracted with ethyl ether and the organic phase washed with brine, dried with $MgSO_4$, and evaporated to afford 12.7 g of a crude oily product. Column

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chromatography (silica gel, ethyl ether–light petroleum) gave 2.86 g (26%) of **6** as an oil: n^{20}_D 1.4990; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.00–1.90 (m, 26 H), 3.40–4.00 (m, 7 H), 4.10–4.35 (m, 2 H), 4.50 (s, 4 H), 7.25 (s, 10 H).

2-Hydroxyethyl 2-Bromohexadecanoate (9). A sample of 10 g (0.02 mol) of **5** dissolved in 100 mL of 95% ethanol was hydrogenated for 3 h at room temperature in the presence of 10% Pd/C (0.5 g). Filtration of the catalyst and evaporation of the solvent afforded 7.8 g (quantitative yield) of **9** as an oil: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.00–1.65 (m, 24 H), 1.80–2.30 (m, 3 H), 3.75 (t, 2 H), 4.10–4.35 (m, 3 H).

3-Tetradecyl-1,4-dioxan-2-one (8). Method A. A solution of 8.36 g (0.0155 mol) of **6** and 1.86 g (0.0465 mol) of NaOH in 40 mL of 50% aqueous ethanol was refluxed for 1 h under magnetic stirring. The solvent was evaporated and the residue dissolved in 20 mL of H_2O, acidified with aqueous 1 M H_2SO_4, and extracted with ethyl ether. The organic phase was dried over $MgSO_4$ and evaporated to give 7.9 g of crude carboxylic acid **7**, which was dissolved in 100 mL of ethanol and hydrogenated over 0.4 g of 10% Pd/C. The catalyst was filtered and the solvent evaporated in vacuo. The residue was dissolved in 100 mL of ethyl ether and washed with H_2O and with brine, and the solvent was evaporated to afford the crude hydroxy acid. On standing overnight it spontaneously gave the lactone **8**, which was crystallized from MeOH to afford 3.69 g (80%) of white solid: mp 79–80 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.00–1.90 (m, 26 H), 3.60–3.90 (m, 3 H), 4.10–4.55 (m, 2 H).

Method B. A solution of 3.79 g (0.01 mol) of **9** in 36 mL of anhydrous toluene was added at room temperature to a stirred suspension of 0.40 g (0.01 mol) of NaH (60% in mineral oil) in 15 mL of toluene. The mixture was refluxed for 48 h, cooled, and acidified with aqueous 1 M H_2SO_4. The aqueous layer was extracted with diethyl ether, and the combined organic phases were dried and evaporated to afford 3.2 g of crude product. Column chromatography (silica gel, ethyl ether–light petroleum) gave 1.13 g (38%) of **8**, mp 79–80 °C.

2-Tetradecyl-3-oxapentane-1,5-diol (10). A solution of 5.46 g (0.0183 mol) of **8** in 50 mL of anhydrous THF was added dropwise to a stirred suspension of 2.78 g (0.0732 mol) of $LiAlH_4$ in 100 mL of THF, and then the mixture was left overnight at room temperature. After careful addition of water and acidification with aqueous 1 M H_2SO_4, THF was evaporated in vacuo, and the aqueous phase was extracted with $CHCl_3$ to give 5.24 g of crude oily product. Column chromatography (silica gel, ethyl ether-light petroleum) afforded 5.0 g (90%) of **10** as as oil; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.00–1.80 (m, 26 H), 3.20–3.90 (m, 9 H).

2-Tetradecyl-3-oxapentane-1,5-diol Bis(methanesulfonate) (11). A solution of 10.64 g (0.092 mol) of methanesulfonyl chloride in 10 mL of anhydrous pyridine was added dropwise to a stirred solution of 9.3 g (0.031 mol) of **10** in 40 mL of pyridine, keeping the temperature below 0 °C. The reaction mixture was kept overnight at this temperature and then poured in ice-cold aqueous 3 N HCl. Extraction with ethyl ether afforded 12.0 g of a yellow thick oil, which was treated with *n*-pentane to give 10.0 g (67%) of **11** as a white solid: mp 60–61 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.00–1.90 (m, 26 H), 3.05 (s, 6 H), 3.50–3.90 (m, 3 H), 4.10–4.40 (m, 4 H).

2-Tetradecyl-1,5-dichloro-3-oxapentane (12). A solution of 3.8 g (0.032 mol) of thionyl chloride in 10 mL of anhydrous benzene was added dropwise to a stirred solution of 3.6 g (0.012 mol) of **10** and 1.92 g (0.024 mol) of anhydrous pyridine in 30 mL of benzene, keeping the temperature below 10 °C. The mixture was refluxed overnight, then poured in ice, acidified with aqueous 3 N HCl, and extracted with ethyl ether. The organic phase was washed with H_2O, dried over $MgSO_4$, and evaporated to afford 4.0 g of a brown oil. Column chromatography (silica gel, light petroleum) gave 3.74 g (92%) of **12** as an oil: n^{20}_D 1.4611; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.00–1.70 (m, 26 H), 3.30–3.95 (m, 7 H).

3-Oxapentane-1,5-diamine (16). A mixture of 31.2 g (0.45 mol) of NaN_3 and 0.83 g (0.005 mol) of KI in 75 mL of H_2O and 5.08 g (0.01 mol) of hexadecyltributylphosphonium bromide in 28.6 g (0.2 mol) of 1,5-dichloro-3-oxapentane was refluxed and stirred for 17 h. The reaction mixture was separated and the aqueous phase extracted with ethyl ether. The combined organic solution was dried ($MgSO_4$), and the solvent was evaporated in vacuo at 25 °C to give 33.44 g of crude diazide (**15**). The latter was dissolved in 250 mL of 95% ethanol and hydrogenated at 25 °C and 30 atm in the presence of 10% Pd/C (3.34 g). Filtration of the catalyst, evaporation of the solvent, and distillation gave 16.8 g (81%) of **16**: bp 55–60 °C (2 torr); n^{23}_D 1.4578 [lit.[2] bp 48–50 °C (1 torr)].

Diethyl 4-Tetradecyl-3,6-dioxaoctane-1,8-dicarboxylate (20). A solution of 17.37 g (0.0465 mol) of carboxylic acid **19** and 0.44 g (0.0023 mol) of *p*-toluenesulfonic acid in 150 mL of absolute ethanol and 150 mL of benzene was refluxed for 24 h, with continuous circulation of condensed vapors through anhydrous Na_2SO_4. After evaporation of the solvent, the residue was dissolved in 200 mL of ethyl ether, washed with aqueous $NaHCO_3$ and water, dried over $MgSO_4$, and evaporated to afford 20.5 g of crude product. Column chromatography (silica gel, ethyl ether–light petroleum) gave 14.0 g (70%) of **20** as a waxy solid: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.00–1.80 (m, 32 H), 3.40–3.75 (m, 3 H), 4.00–4.35 (m, 8 H).

4-Tetradecyl-3,6-dioxaoctane-1,8-diol (21). A solution of 12.23 g (0.0285 mol) of **20** in 50 mL of anhydrous ethyl ether was added dropwise to a stirred suspension of 1.51 g (0.040 mol) of $LiAlH_4$ in 160 mL of ethyl ether. The mixture was refluxed for 2 h. The excess of $LiAlH_4$ was destroyed with ethyl acetate, water and aqueous 1 M H_2SO_4 were added, and the aqueous phase was extracted with ethyl ether to afford 9.80 g (quantitative yield) of **21** as a waxy solid: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.00–1.70 (m, 26 H), 3.40–3.95 (m, 13 H).

4-Tetradecyl-3,6-dioxaoctane-1,8-diol Bis(methanesulfonate) (18). A solution of 9.61 g (0.084 mol) of methanesulfonyl chloride in 10 mL of anhydrous pyridine was added dropwise to a stirred solution of 9.70 g (0.028 mol) of **21** in 90 mL of pyridine, keeping the temperature below 0 °C. The reaction mixture was left overnight under these conditions and then poured in ice-cold aqueous 3 N HCl. Extraction with ethyl ether afforded 13.0 g of crude product, which was treated with *n*-pentane to give 9.23 g (65%) of **18** as a waxy white solid: mp 40–41 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.00–1.70 (m, 26 H), 3.05 (s, 6 H), 3.40–3.95 (m, 7 H), 4.35 (t, 4 H).

$[H^+\subset(1.1.1,C_{14})]I^-$ (3, X = I). A sample of 2 mmol of the appropriate base was added to a well-stirred solution of 0.344 g (2 mmol) of **4** in 10 mL of anhydrous THF in an argon atmosphere at room temperature. The mixture was stirred for 2 h, and then a solution of 2 mmol of **11** or **12** in 10 mL of THF was added. The reaction mixture was stirred at room temperature for 18 h and then refluxed for an additional 48 h. The solvent was evaporated, and the residue was taken up with 150 mL of CH_2Cl_2 and 50 mL of H_2O; the organic phase was shaken several times with 20-mL portions of saturated aqueous KI solution and dried over $MgSO_4$. Evaporation of the solvent in vacuo, followed by column chromatography (neutral alumina, $CHCl_3$–MeCN) gave pure **3** (X = I) (29–43% yield, see Table I) as a white solid: mp 65–67 °C (cyclohexane); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.00–1.70 (m, 26 H), 2.70–3.10 (m, 6 H), 3.15–4.00 (m, 17 H), 8.80 (br s, 1 H, no exchange with D_2O); MS, m/z 441 (M^+). When Na_2CO_3 was used as base, the reaction mixture was stirred and refluxed for 4 days and then worked as described above to afford **3** (X = I) in 21% yield.

$[H^+\subset(1.1.1)]OMes^-$ (2, X = OMes). It was obtained following the same procedure used for **3**. The complex is insoluble in the boiling reaction mixture. At the end of the reaction the precipitate was filtered under nitrogen and the product separated from $MesO^-Li^+$ by continuous extraction with boiling 1,2-dichloroethane. The pure cryptate **2** (X = OMes) was isolated as a white solid in 40% yield by the addition of *n*-pentane: mp >250 °C; ^{1}H NMR (D_2O) δ 2.60 (s, 3 H), 3.10 (m, 12 H), 3.52 (t, 12 H), 9.60 (br s, 1 H).

General Procedure for the Synthesis of [2.2.1] and [2.2.2] Cryptates (Table I, Entries 6–13). Diazacoronand **22** or **23**, bis(methanesulfonate) **17** or **18**, and the appropriate base were refluxed in anhydrous THF for 4 days. Filtration of the precipitate and evaporation of the solvent gave a residue, which was dissolved in $CHCl_3$. This solution was shaken with a 10 molar excess of the appropriate solid iodide for 15 h, then filtered, and evaporated. Column chromatography (silica gel, MeCN–$CHCl_3$) afforded crude cryptates, which were generally crystallized from CH_2Cl_2–diethyl ether. The cryptates showed physical properties (^{1}H NMR, mp)

identical with those of samples obtained from the cryptand and alkaline iodide. Their purity (95–100%) was also tested by potentiometric titration of iodide ion. [2.2.2,C_{14}] was isolated as the free cryptand after decomplexation in an acidic medium and the addition of LiOH (entry 13).

Registry No. 2 (x = OMes), 80322-79-8; 3 (X = I), 92958-34-4; 3 (free base), 80322-80-1; 4, 294-92-8; 5, 97431-31-7; 6, 97431-32-8; 7, 97431-35-1; 7·Na, 97431-34-0; 8, 6005-35-2; 9, 97431-33-9; 10, 97431-37-3; 11, 80322-78-7; 12, 97431-38-4; 13, 34604-52-9; 15, 24345-74-2; 16, 2752-17-2; 17, 80322-82-3; 18, 80322-83-4; 19, 56741-58-3; 20, 97431-39-5; 21, 60742-62-3; 22, 31249-95-3; 23, 23978-55-4; 24, 31364-42-8; 24 (Li complex), 57064-20-7; 24 (Na complex), 57064-16-1; 24 (K complex), 97467-01-1; 25, 97431-40-8; 25 (Na complex), 97485-93-3; 26, 23978-09-8; 26 (K complex), 97485-94-4; 26 (Na complex), 97485-95-5; 27, 64066-13-3; $CH_3(CH_2)_{13}CH(CO_2H)OCH_2CH_2OH$, 97431-36-2; diglycolic acid dichloride, 21062-20-4; 2-bromopalmitoyl chloride, 69319-95-5; 2-(benzyloxy)ethanol, 622-08-2; methanesulfonyl chloride, 124-63-0; 1,5-dichloro-3-oxapentane, 111-44-4.

Clavalanine (Ro 22-5417), a New Clavam Antibiotic from *Streptomyces clavuligerus*. 4. A Stereorational Synthesis

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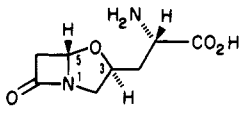
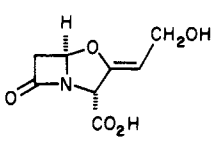
Clavalanine (Ro 22-5417), a new β-lactam antibiotic, 3-[(3*S*,5*S*)-7-oxo-1-aza-4-oxabicyclo[3.2.0]hept-3-yl]-L-alanine (**1**), was synthesized by a route in which D-xylose (**4**) supplied the stereochemical requirements. From **4** was elaborated a (2*S*,4*S*)-2-amino-4,5-dihydroxypentanoic acid derivative (**16**), which was condensed with 4-acetoxy-2-azetidinone (**3**) to afford with good diastereoselectivity, after final removal of protecting groups, the desired clavam **1**.

Streptomyces clavuligerus is known as a prolific producer of β-lactam antibiotics.[1] The latest creation of this organism to have been discovered is the clavam antibiotic clavalanine (Ro 22-5417), the complete structure of which has been determined as 3-[(3*S*,5*S*)-7-oxo-1-aza-4-oxabicyclo[3.2.0]hept-3-yl]-L-alanine (**1**).[2-4] Thus, in contrast to



1



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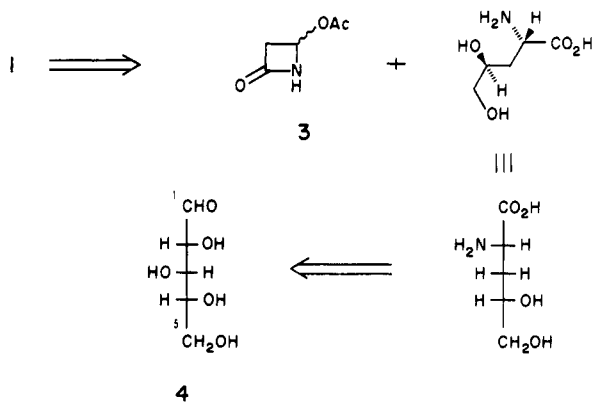
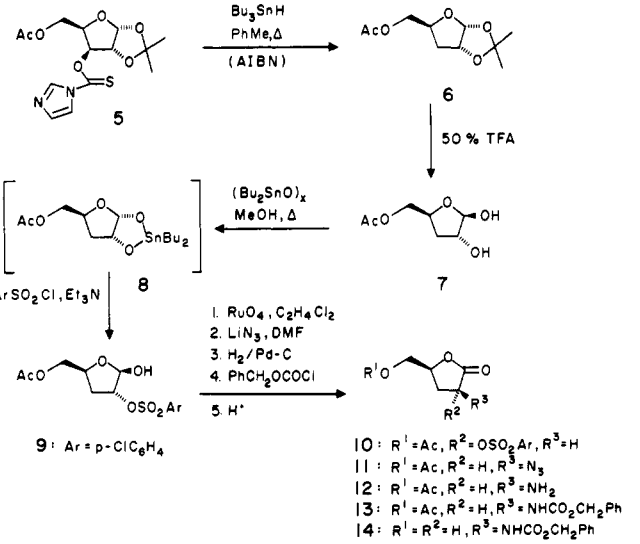
all the previously isolated β-lactams of *S. clavuligerus* such as penicillin N, desacetoxycephalosporin C, cephamycin C, and, most notably in this context, clavulanic acid (**2**), in all of which the carbon atom joining the bicyclic ring system has the *R* configuration, the new congener possesses *S* stereochemistry at the ring juncture.[4] Presumably as a consequence of this profound stereochemical difference, clavalanine (**1**) does not exert its antimicrobial activity, like the other β-lactams, via inhibition of bacterial cell wall synthesis; it is also neither substrate nor inhibitor of β-lactamases. Rather, **1** is an antimetabolite of *O*-succinylhomoserine and as such it intervenes in the biosynthesis of methionine.[2]

We have now completed a synthesis of clavalanine (**1**), which provides unequivocal confirmation of its absolute stereochemistry, previously assigned mainly on the basis of chiroptical and other spectral measurements.[4] Retrosynthetic analysis, following the train outlined in Scheme I, led us to a plan whereby the β-lactam portion of **1** would be obtained from 4-acetoxy-2-azetidinone (**3**) and the remaining five-carbon fragment would come from a carbohydrate. The choice of D-xylose (**4**) for this purpose would ensure the correct chirality at C-3 of **1** and allow the elaboration of that at the α-carbon of the amino acid side chain. While the stereochemistry at C-5, the ring junction,

Scheme I



Scheme II



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