FEATURE ARTICLE

Ruthenium-Catalyzed Oxidations for Selective Syntheses of Ketones and Acyl Cyanides. Selective Acylation of Amino Compounds with Acyl Cyanides

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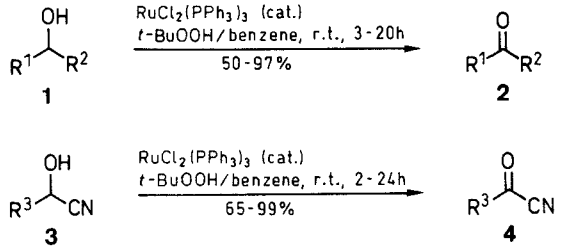
Oxidation of alcohols to the corresponding carbonyl compounds with *tert*-butyl hydroperoxide in the presence of dichlorotris(triphenylphosphine)ruthenium catalyst gives the corresponding carbonyl compounds with high efficiency. This method can be applied to the oxidation of cyanohydrins to give acyl cyanides which are versatile synthetic intermediates. Acylation of amino compounds with acyl cyanides thus obtained proceeds chemoselectively. Thus, the reaction of amino alcohols with acyl cyanides gives *N*-acylated products exclusively. In the similar *N*-acylation of polyamines primary amines are selectively acylated in the presence of secondary amines. These reactions are highly useful for the synthesis of spermidine and spermine alkaloids such as spermidine siderophores. Dimeric cyclocoupling reaction of diacyl cyanides such as iso- and terephthaloyl cyanides with polyamines can be performed under the similar reaction conditions to give the corresponding polyazamacrocycles with high efficiency.

Cytochrome P-450 monooxygenase is one of the most attractive metalloenzymes, which catalyzes specific oxidations of a variety of organic substrates in xenobiotic metabolism.[1] Because of its interest from bioorganic and bioinorganic viewpoints several model reactions using metalloporphyrins have been reported.[2] We have explored the simulation of enzymatic functions of metabolism of amines with transition-metal catalysts,[3] and found that the low-valent ruthenium catalyst/peroxide system is effective for P-450 type oxygenations of various substrates such as amines,[4] amides,[5] nitriles,[6] and hydrocarbons.[7] In these reactions the catalytically active species seems to be a low-valent oxoruthenium complex which undertakes abstraction of hydrogen atom from a variety of unactivated substrates as a crucial step.[3] The oxidation of alcohols with low-valent oxoruthenium species has been studied mechanistically.[8] Therefore, the oxidation of alcohols by using our catalytic system has been studied extensively. We have found that such catalytic systems have been proven to be efficient for the oxidation of hydroxy compounds.[9] Thus, the oxidation of alcohols **1** with *tert*-butyl hydroperoxide (*t*-BuOOH) in the presence of dichlorotris(triphenylphosphine)ruthenium(II) [$RuCl_2(PPh_3)_3$] catalyst proceeds under mild conditions to give the corresponding ketones **2** efficiently. This oxidation can also be applied to the transformation of cyanohydrins **3** to acyl cyanides **4** which are versatile synthetic intermediates.

The synthetic utilities of these oxidation reactions have been illustrated by the selective acylations of amino compounds with acyl cyanides thus obtained. The reaction of amino alcohols with acyl cyanides gives selectively *N*-acylated amino alcohols.[9] Furthermore, primary amines are selectively acylated in the presence of secondary amines.[10] This reaction provides a versatile method for a short-step synthesis of nitrogen containing natural products such as spermidine and spermine alkaloids. Extension of the latter reaction disclosed highly efficient method for the synthesis of polyazamacrocycles which are of importance in view of binding properties with various guest species.

Details of these reactions are described with respect to scope, mechanism, and synthetic applications.

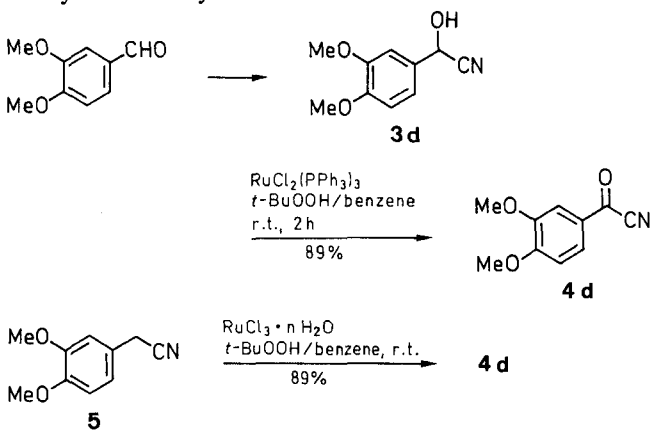


Ruthenium-catalyzed oxidation of alcohols with *t*-BuOOH proceeds under mild conditions to give the corresponding carbonyl compounds. Although ruthenium-catalyzed oxidations of alcohols have been performed by using various oxidants such as sodium periodate,[11] sodium bromate,[12] *N*-methylmorpholine *N*-oxide,[13] iodosylbenzene,[14] bis(trimethylsilyl) peroxide,[15] oxygen,[16] and allyl methyl carbonate,[17] our method provides a convenient method for the oxidation of alcohols with respect to simple operation, mild reaction conditions, and high efficiency.

The catalytic activities of ruthenium complexes for the oxidative transformation of 1-phenylethanol (**1a**) to acetophenone (**2a**) were examined. $RuCl_2(PPh_3)_3$ has been proven to be the most effective catalyst (conversion of **1a** 94%, yield of **2a** 100%).[18] Other catalysts such as ruthenium(III) chloride hydrate ($RuCl_3 \cdot nH_2O$) and dihydridotetrakis(triphenylphosphine)ruthenium(II) [$RuH_2(PPh_3)_4$] gave satisfactory results (83%, 100%; 82%, 97%). The representative results of the catalytic oxidation of various alcohols with *t*-BuOOH are shown in Table 1. Aliphatic, aromatic, and allylic alcohols are converted into the corresponding carbonyl compounds. Methyl mandelate also undergoes the oxidation to give the corresponding 1,2-dicarbonyl compounds.

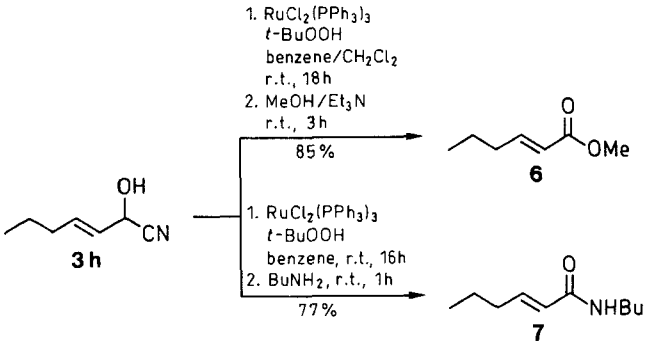
The present oxidation can be applied to the synthesis of acyl cyanides from the corresponding aldehyde cyanohydrins. Acyl cyanides are versatile synthetic intermediates and have been utilized in a variety of transformations of CO and CN functions,[19] nucleophilic reactions with enolates,[20] Michael additions,[21] and metal-catalyzed decarbonylation reactions.[22] Acyl cyanides have been prepared by condensation of acid halides with a variety of

metal cyanides[23] or cyanotrimethylsilane.[24] An alternative method is the oxidation of cyanohydrins with oxidants such as chromium(VI) oxide,[25] and manganese(IV) oxide.[26] The latter method is convenient for the conversion of sensitive aldehydes into esters, although acyl cyanides are not isolated.[26] *O*-Silylated cyanohydrins are also oxidized upon treatment with bromine[27] and pyridine dichromate[28] to give acyl cyanides. The present reaction is advantageous over the previous methods because of its high efficiency and facile isolation of the products. Typically, oxidation of 3,4-dimethoxybenzaldehyde cyanohydrin **3d** with two equivalents of *t*-BuOOH in dry benzene at room temperature gives 3,4-dimethoxybenzoyl cyanide **(4d)** in 89% yield. It is noteworthy that the same acyl cyanide **4d** can be obtained by catalytic oxidation of (3,4-dimethoxyphenyl)acetonitrile **(5)** with *t*-BuOOH in the presence of $RuCl_3 \cdot nH_2O$ catalyst in 89% yield.[6]

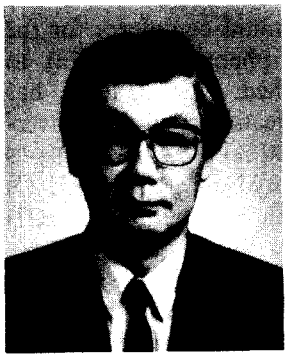


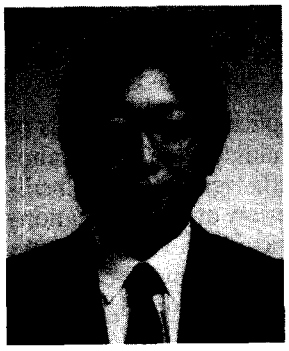
The representative results of the formation of acyl cyanides are summarized in Table 2. Aromatic and α, β-unsaturated cyanohydrins have been efficiently converted into the corresponding acyl cyanides irrespective of substituents on aryl groups. The oxidation of α,β-unsaturated aldehyde cyanohydrins proceeds slowly, and hence *t*-BuOOH should be added for 5–6 hours. Aliphatic aldehyde cyanohydrins were converted into the corresponding carboxylic acids under the reaction conditions by hydrolysis of unstable acyl cyanides formed.

Since acyl cyanides can be smoothly converted into a variety of carboxylic acid derivatives,[19] the reaction provides a convenient method for the synthesis of acid derivatives from sensitive aldehydes. Typically, the ruthenium-catalyzed oxidation of 2-hydroxy-3-heptenenitrile **(3h)** followed by treatment with methanol in the presence of triethylamine afforded the corresponding methyl ester **6** in 85% yield. Similar treatment with butylamine gave *N*-butylamide **7** in 77% yield.



The present oxidation can be rationalized by assuming the mechanism as shown. The reaction of Ru(II) complex with *t*-BuOOH would give Ru(II)OO-*t*-Bu which undergoes heterolytic cleavage of the O–O bond to give oxoruthenium(IV) intermediate **8**.[8,29] Intermediacy of oxoruthenium(IV) species in the ruthenium(II)/peroxide catalytic systems has been confirmed by the $RuCl_2(PPh_3)_3$-catalyzed oxidation of tertiary amines with *t*-BuOOH. The kinetic experiments such as Hammett treatment and inter- and intramolecular deuterium isotope effects indicate that the reaction proceeds via P-450 type mechanism which involves oxoruthenium(IV) species as a key intermediates.[4]





Bibliographic Sketches

Shun-Ichi Murahashi (born in Osaka, Japan in 1937) received his Ph.D. degree in 1967 from Osaka University. In 1963 he was appointed as Assistant Professor of Osaka University. He served as a research associate at Columbia University from 1968 to 1970 under the direction of Prof. Ronald Breslow. In 1972 he became Associate Professor, and since 1979 he has been a Professor of Organic Chemistry.

Takeshi Naota (born in Osaka, Japan in 1957) received his Ph.D. degree in 1988 from Osaka University, where he is currently Assistant Professor of Organic Chemistry. From 1990 to 1991 he did postdoctoral work with Prof. Barry M. Trost at Stanford University.

Table 1. Catalytic Oxidation of Alcohols **1** to Ketones **2**

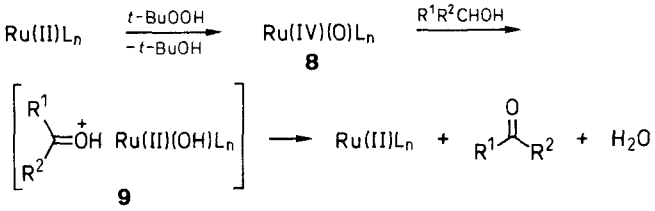
Product	R^1	R^2	Time (h)	Yield[a] (%)	Molecular Formula[b]	mp (°C)
2a	Ph	Me	3	90	C_8H_8O (120.2)	liquid
2b	Ph	Ph	3	95	$C_{13}H_{10}O$ (183.2)	49–50
2c	Bn	Me	20	50	$C_9H_{10}O$ (134.2)	liquid
2d	*trans*-PhCH=CH	Me	3	51	$C_{10}H_{10}O$ (146.2)	41
2e	*trans*-MeCH=CH	n-C_5H_{11}	3	57	$C_9H_{16}O$ (140.2)	liquid
2f	Ph	CO_2Me	17	96	$C_9H_8O_3$ (164.2)	liquid

[a] All yields are of pure products, isolated by column chromatography.
[b] Satisfactory microanalyses obtained for all compounds.

Table 2. Conversions of Cyanohydrins **3** to Acyl Cyanides **4**

Product	R^3	Time (h)	Yield[a] (%)	Molecular Formula[b]	mp (°C)
4a	Ph	3	87	C_8H_5NO (131.1)	liquid
4b	4-MeC_6H_4	3	99	C_9H_7NO (145.1)	49–50
4c	2-$MeOC_6H_4$	11	82	$C_9H_7NO_2$ (161.1)	67–68
4d	3,4-$(MeO)_2C_6H_3$	2	89	$C_{10}H_9NO_3$ (191.2)	110
4e	3-BnO-4-$MeOC_6H_3$	15	87	$C_{16}H_{13}NO_3$ (267.3)	102–103
4f	4-$PhCO_2C_6H_4$	5	80	$C_{15}H_9NO_3$ (251.2)	118–119
4g	1-naphthyl	24	65	$C_{12}H_7NO$ (181.2)	98–100
4h	*trans*-C_3H_7CH=CH	8	81	C_7H_9NO (123.1)	liquid

[a] All yields are of pure products, isolated by column chromatography.
[b] Satisfactory microanalyses obtained for all compounds.



The ruthenium complex **8** abstracts an α-hydrogen atom of alcohols or cyanohydrins to afford $[R^1R^2(OH)C \cdot Ru(III)(OH)]$, which undergoes one electron transfer to give intermediate **9**. Alternatively, the oxidation of alcohols would occur by a two electron, hydride transfer to produce **9**.[8] The intermediate **9** is converted into Ru(II), carbonyl compounds, and water to complete the catalytic cycle. The mechanism which involves radical chain reactions induced by homolytic cleavage of *t*-BuOOH[30] seems unlikely, because i) oxidation of benzylic positions does not occur, and ii) radical coupling products could not be detected among the products.

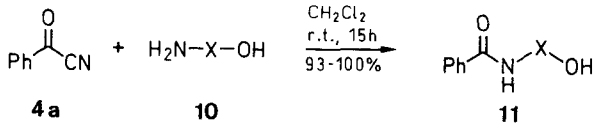
Substantial effort has been devoted to find reagents for selective protection of amine functions.[31] We have found that acyl cyanides are highly useful reagents for this purpose. Thus, the reaction of amino alcohols **10** with benzoyl cyanides **(4a)** gives selectively *N*-benzoylated products **11**.[9] Similar treatment of polyamines **12** with **4a** gives *N*-acylated products **13** in which primary amino

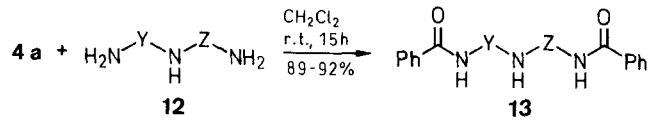
Table 3. Compounds **2** and **4** Prepared

Product	IR (Nujol) ν (cm^{-1})	^1H NMR (solvent)[a] δ, J (Hz)
2a	1670	2.57 (s, 3H), 7.25–7.60 (m, 3H), 7.77–8.08 (m, 2H)
2b	1660	7.18–7.58 (m, 6H), 7.65–7.85 (m, 4H)
2c	1710	2.00 (s, 3H), 3.53 (s, 2H), 7.17 (s, 5H)
2d	1665	2.27 (s, 3H), 6.58 (d, J = 16, 1H), 7.15–7.73 (m, 5H), 7.42 (d, J = 16, 1H)
2e	1675	0.60–2.10 (m, 9H), 1.88 (d, J = 6, 3H), 2.28 (t, J = 6, 2H), 6.00 (d, J = 15, 1H), 6.73 (dq, J = 15, 6, 1H)
2f	1740, 1690	3.92 (s, 3H), 7.27–7.70 (m, 3H), 7.77–8.10 (m, 2H)
4a	2230, 1680	7.25–7.83 (m, 3H), 8.00–8.67 (m, 2H)
4b	2225, 1670	2.49 (s, 3H), 7.40 (d, J = 8.1, 2H), 8.04 (d, J = 8.1, 2H)
4c	2230, 1665	4.08 (s, 3H), 7.08 (d, J = 8.5, 1H), 7.14 (ddd, J = 7.8, 7.3, 0.98, 1H), 7.59 (ddd, J = 8.5, 7.3, 1.7, 1H), 8.18 (dd, J = 7.8, 1.7, 1H)
4d	2225, 1670	3.96 (s, 3H), 4.02 (s, 3H), 7.03 (d, J = 8.5, 1H), 7.53 (d, J = 2.0, 1H), 7.88 (dd, J = 8.5, 2.0, 1H)
4e	2225, 1670	3.97 (s, 3H), 5.15 (s, 2H), 6.97 (d, J = 8, 1H), 7.25–7.50 (m, 5H), 7.53 (d, J = 2, 1H), 7.80 (dd, J = 8, 2, 1H)
4f	2220, 1660	7.23–7.70 (m, 3H), 7.40 (d, J = 8.5, 2H), 8.00–8.30 (m, 2H), 8.13 (d, J = 8.5, 2H)
4g	2220, 1655	7.30–8.07 (m, 4H), 8.22 (d, J = 7, 1H), 8.53 (dd, J = 7, 2, 1H), 9.10 (dd, J = 7, 2, 1H)
4h	2230, 1680	1.00 (t, J = 6, 3H), 1.62 (tq, J = 6, 7, 2H), 2.42 (dt, J = 6, 7, 2H), 6.20 (d, J = 16, 2H), 7.40 (dt, J = 16, 6, 1H)

[a] **2a–e** in CCl_4, **2f**, **4** in $CDCl_3$.

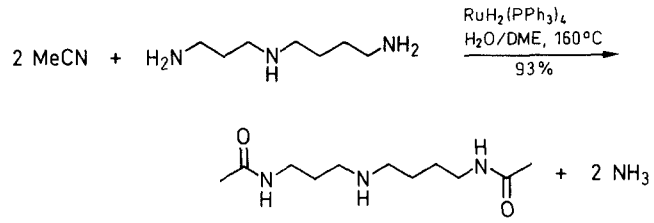
groups are selectively acylated in the presence of secondary amino groups.[10]



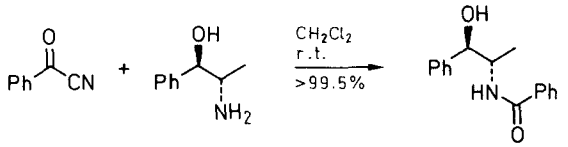


In the chemistry of amino sugars[32] and oligonucleotides,[33] many methods for selective *N*-acylation in the presence of hydroxy groups have been explored; however, the reported methods often lack generality. Selective protections of amino alcohols are limited to few reactions which include *N*-acylation with pentafluorophenyl acetate,[34] poly(3-acyl-2-oxazolone),[35] 2,5-dihydro-2-oxo-oxazolylphosphonate,[36] and 3-acyl-1,3-thiazolidine-2-thione,[37] and *N*-tosylation with *N*-methyl-*N*-tosylpyrrolidinium perchlorate.[38]

Selective protection and functionalization of polyamines are of particular importance in view of synthesis of naturally occurring polyamines such as spermidine and spermine alkaloids[39] which have potent antibiotic[40] and antineoplastic[41] properties. Several direct[35–37,42] and multistep[39,43] methods for protection of polyamines have been reported. The present acylation reaction is advantageous over the previous methods because i) the reaction is general and selective; ii) the product isolation is simple, and iii) a variety of acyl cyanides can be readily prepared by either the ruthenium-catalyzed oxidation of cyanohydrins or nitriles.[6] It is noteworthy that $RuH_2(PPh_3)_4$ catalyzed acylation of primary amines with nitriles proceeds chemoselectively in the presence of secondary amines.[44]



The effects of solvents and reaction temperatures were examined for the reaction of 3-amino-1-propanol with benzoyl cyanide (**4a**). The products detected during the reaction are *N*-benzoylated product, *N*-(3-hydroxypropyl)benzamide (**11a**) (84–93%) and *N,O*-dibenzoylated product, 3-benzamidopropyl benzoate (0–6%). Dichloromethane seems to be the best solvent. The other aprotic solvents such as chloroform, dimethylformamide and 1,2-dimethoxyethane also gave satisfactory results. By using acetonitrile or benzene, the yield of **11a** became low. The reaction proceeds at room temperature. Low temperatures do not influence the selectivity significantly. The detectable byproducts in these reactions are small amounts of *N,O*-dibenzoylated products (0–3%) which can be readily removed by recrystallization or chromatographic separation.



Typically the reaction of (1*R**,2*R**)-2-amino-1-phenyl-1-propanol (**10e**) with **4a** in dichloromethane at room temperature gave (1*R**,2*R**)-*N*-[(2-phenyl-2-hydroxy-1-methyl)ethyl]benzamide (**11e**) in >99.5% yield. The representative results of the selective *N*-acylation of various amino alcohols with **4a** are summarized in Table 4.

Table 4. Selective *N*-Benzoylation of Amino Alcohols **10**

Product	X	Yield[a] (%)	Molecular Formula[b]	mp (°C)
11a	$(CH_2)_3$	93	$C_{10}H_{13}NO_2$ (179.2)	oil
11b	$(CH_2)_5$	95	$C_{12}H_{17}NO_2$ (207.3)	oil
11c	$CH_2CH(CH_3)$	97	$C_{10}H_{13}NO_2$ (179.2)	89–90
11d	$CH_2CH(Ph)$	98	$C_{15}H_{15}NO_2$ (241.3)	146–147
11e	(1*R**,2*R**)-$CH(CH_3)CH(Ph)$	>99.5	$C_{16}H_{17}NO_2$ (255.3)	142–143

[a] All yields are of pure products, isolated by column chromatography.
[b] Satisfactory microanalyses obtained for all compounds.

Table 5. Selective *N*-Benzoylation of Polyamine **12**

Product	Y	Z	Yield[a] (%)	Molecular Formula[b]	mp (°C)
13a	$(CH_2)_2$	$(CH_2)_2$	89	$C_{18}H_{21}N_3O_2$ (311.4)	108–109
13b	$(CH_2)_3$	$(CH_2)_4$	92	$C_{21}H_{27}N_3O_2$ (353.4)	130–131
13c	$(CH_2)_3$	$(CH_2)_4NH(CH_2)_3$	91	$C_{24}H_{34}N_4O_2$ (410.5)	112

[a] All yields are of pure products, isolated by column chromatography.
[b] Satisfactory microanalyses obtained for all compounds.

Acylation of primary amines of polyamines can be performed in the presence of secondary amines under similar reaction conditions. The representative results of the reaction of polyamines with **4a** are summarized in Table 5. Linear polyamines such as spermidine and spermine are acylated with various acyl cyanides. The acylation with alkanoyl cyanides proceeds quite rapidly even at −78 °C and results in lower selectivity (70–80%).

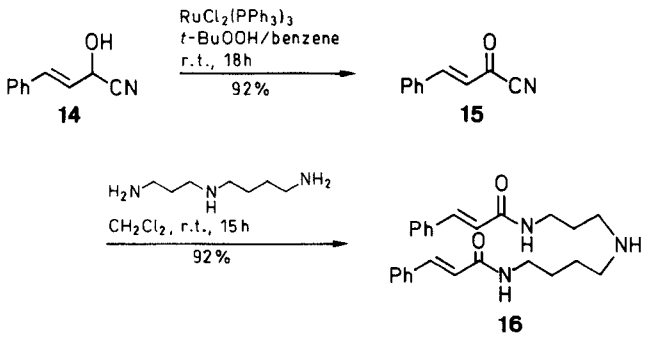
The efficiency of the present reaction is illustrated by the synthesis of maytenine [N^1,N^8-bis(*trans*-cinnamoyl)spermidine][45] (**16**) which has been isolated from *Maytenus chuchuhuasha*. Thus, the $RuCl_2(PPh_3)_3$-catalyzed oxidation of *trans*-cinnamaldehyde cyanohydrin **14** with *t*-BuOOH gave *trans*-cinnamoyl cyanide (**15**) in 92%

Table 6. Compounds **11** and **13** Prepared

Product	IR (Nujol) ν (cm^{-1})	^1H NMR (solvent)[a] δ, J (Hz)
11a	3300, 1640	1.74 (tt, J = 5.9, 6.4, 2H), 3.52 (dt, J = 6.4, 6.1, 2H), 3.65 (t, J = 5.9, 2H), 4.13 (br, 1H), 7.32 (dddd, J = 7.3, 6.8, 1.5, 1.5, 2H), 7.42 (tt, J = 7.3, 1.5, 1H), 7.76 (dd, J = 6.8, 1.5, 2H), 7.68–7.80 (br, 1H)
11b	3270, 1635	1.17–1.83 (m, 6H), 3.00 (br, 1H), 3.17–3.77 (m, 4H), 6.87 (br, 1H), 7.10–7.53 (m, 3H), 7.53–7.85 (m, 2H)
11c	3250, 1640	1.21 (d, J = 6.1, 3H, Me), 3.12 (br, 1H, OH), 3.28 (ddd, J = 13.9, 7.6, 5.1, 1H), 3.62 (ddd, J = 13.9, 6.5, 2.9, 1H), 4.00 (qdd, J = 6.1, 6.5, 2.9, 1H), 6.98 (br, 1H), 7.38 (dddd, J = 7.3, 6.8, 1.5, 1.5, 1H), 7.48 (tt, J = 7.3, 1.5, 1H), 7.77 (dd, J = 6.8, 1.5, 1H)
11d	3300, 1610	3.46 (ddd, J = 13.3, 7.8, 5.5, 1H), 3.63 (ddd, J = 13.3, 5.7, 5.5, 1H), 4.93 (br, 1H), 5.66 (br s, 1H), 7.35 (tt, J = 7.0, 1.7, 1H), 7.39–7.65 (m, 7H), 7.97 (dd, J = 8.0, 1.7, 2H), 8.64 (t, J = 5.5, 1H)
11e	3350, 1615	1.10 (d, J = 6.8, 3H), 4.16 (qd, J = 6.8, 4.8, 1H), 4.71 (dd, J = 4.8, 4.6, 1H), 5.45 (d, J = 4.6, 1H), 7.19 (dt, J = 1.5, 7.1, 1H), 7.30 (t, J = 7.1, 2H), 7.35–7.53 (m, 5H), 7.77 (dt, J = 6.6, 1.5, 2H), 8.20 (d, J = 8.6, 1H)
13a	3320, 1640	3.13 (t, J = 6, 4H), 3.30–3.75 (br, 1H), 3.60 (dt, J = 5, 6, 4H), 7.46 (dd, J = 7, 7, 4H), 7.54 (t, J = 7, 2H), 7.94 (d, J = 7, 4H), 8.82 (t, J = 5, 2H)
13b	3270, 1630	1.47–1.77 (m, 6H), 1.83 (s, 1H), 2.70 (dt, J = 6, 6, 4H), 3.47 (t, J = 6, 4H), 6.80 (br, 2H), 7.22–7.47 (m, 6H), 7.47–7.93 (m, 4H)
13c	3250, 1625	1.13–2.03 (m, 8H), 2.23 (s, 2H), 2.40–3.00 (m, 4H), 3.10–3.73 (m, 8H), 7.10–7.53 (m, 6H), 7.53–7.90 (m, 4H), 8.00 (br, 2H)

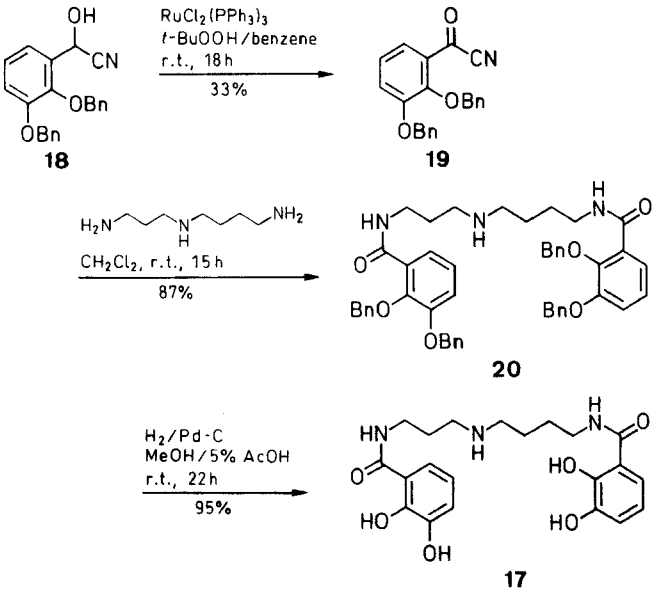
[a] **11a–c**, **13b–c** in $CDCl_3$, **11d–e**, **13a** in DMSO-d_6.

yield. The reaction of spermidine with two equivalents of **15** in dry dichloromethane at room temperature gave **16** in 92% yield. Although maytenine has been synthesized by several methods,[37,39b,42c,d,45] our method is easy to carry out with fine selectivity.

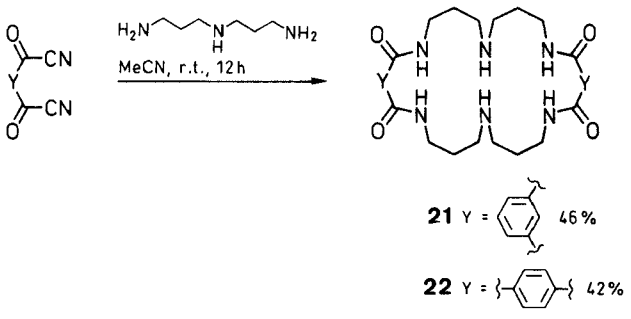


Importantly, the present method is useful for the synthesis of spermidine siderophores[39a] which are a biologically important class of microbially produced iron transport compounds.[46] A typical example is the synthesis of siderophore N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine[47] **(17)** which has been isolated from *Micrococcus denitrificans* and is an important precursor of the spermidine catecholamides such as agrobactin[48] and parabactin.[49] The reaction of spermidine with two equivalents of 2,3-dibenzyloxybenzoyl cyanide **(19)**, derived from cyanohydrin **18**, gave the corresponding bis(benzoyl)spermidine **20** in 87% yield. Removal of benzyl groups by catalytic hydrogenation over palladium on charcoal in methanol/10% acetic acid gave siderophore **17** in 95% yield.

The present reaction is highly useful for a single-step synthesis of macrocyclic polyamines,[50] which have received considerable attention because of their cation[51] and anion[52] binding properties. The reaction of isophthaloyl cyanide with 3,3′-diaminodipropylamine in acetonitrile at room temperature followed by treatment with hydrogen chloride gave 3,7,11,19,23,27-hexaazatricyclo[27.3.1.1.^{13,17}]tetratriaconta-1(32),13,15,17(34),29(33),30-hexa-

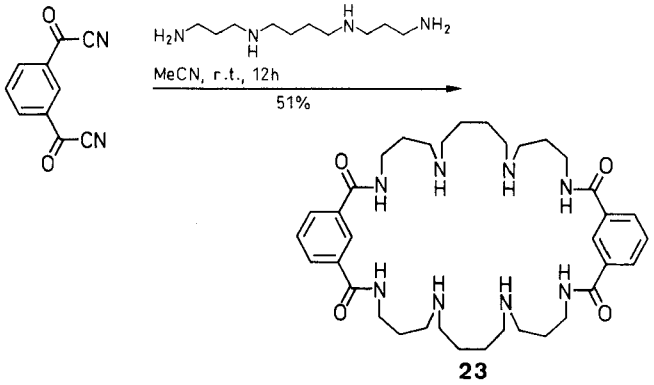


ene-2,12,18,28-tetraone hydrochloride (**21** · 2HCl) in 46% isolated yield. Similar treatment of terephthaloyl cyanide with 3,3′-diaminodipropylamine gave 3,7,11,18,22,26-hexaazatricyclo[26.2.2.2^{13,16}]tetratriaconta-1(31),13,15,28(32),29,33-hexaene-2,12,17,27-tetraone hydrochloride (**22** · 2HCl) in 42% yield.



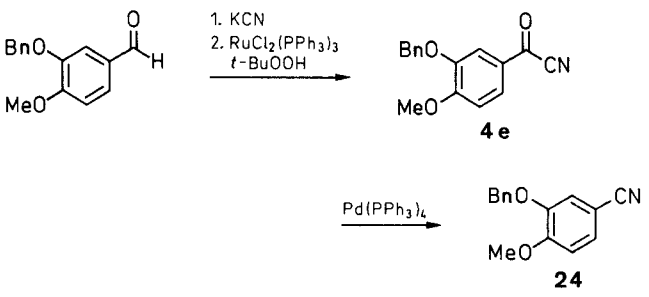
In these reactions only trace amounts of monomeric and trimeric coupling products were isolated. The present reaction provides a convenient and useful method for the synthesis of polyazamacrocyles via dimeric cyclocoupling

of dicarboxylic acid derivatives with polyamines because of its high efficiency, mild reaction conditions, free from protection of secondary amines, and free from the high dilution technique. This is in contrast to the fact that the reaction of diacid chlorides with polyamines gives preferentially monomeric coupling products. For example, the reaction of isophthaloyl dichloride with 3,3'-diaminodipropylamine in acetonitrile at room temperature gave the monomeric coupling product, 3,7,11-triazabicyclo[11.3.1]heptadeca-1(16),13(17),14-triene-2,12-dione (21%) along with many oligomeric coupling products. Similar reactions of diacyl cyanides with tetramines give the corresponding octaazamacrocycles with high efficiency. Thus, the reaction of isophthaloyl cyanide with spermine at room temperature gave 3,7,12,16,24,28,33,37-octaazatricyclo[37.3.1.1^{18,22}]tetratetraconta-1(42),18,20,22(44),39(43),40-hexaene-2,17,23,38-tetraone hydrochloride (**23** · 4HCl) in 51% yield.



23

Finally, it should be noted that the present oxidation reaction provides an efficient method for the synthesis of nitriles from aldehydes under mild and neutral conditions. Typically, the ruthenium-catalyzed oxidation of 3-benzyloxy-4-methoxybenzaldehyde cyanohydrin with *t*-BuOOH gives the corresponding acyl cyanide **4e** in 87% yield. The treatment of **4e** with $Pd(PPh_3)_4$ catalyst gives the decarbonylated[22] nitrile **24** in 99% yield.



4e

24

Cyanohydrins were prepared by the reaction of aldehydes with KCN[53] or with Me_3SiCN.[54] A solution of *t*-BuOOH in dry benzene was prepared and titrated by using the Sharpless method.[55] $RuCl_2(PPh_3)_3$ was prepared according to the reported method.[56] Isophthaloyl cyanide and terephthaloyl cyanide were prepared by the reaction of the corresponding acid chlorides with cuprous cyanide.[57] For all new compounds satisfactory mircoanalyses or HRMS were obtained.

Ruthenium-Catalyzed Oxidation of Alcohols 1 or Cyanohydrins 3 with *t*-BuOOH; General Procedure:

To a stirred solution of alcohol **1** or cyanohydrin **3** (2 mmol), $RuCl_2(PPh_3)_3$ (0.1 mmol) in dry benzene (4.0 mL) was added a 3.45 M solution of *t*-BuOOH in dry benzene (1.2 mL, 4.0 mmol) dropwise at r.t. over a period of 1 h. After stirring for the appropriate time (see Table 1 or 2), palladium black or $NaHSO_3$ was added to decompose excess *t*-BuOOH. The solvent was removed under reduced pressure, and the product was purified by column chromatography (ketone: alumina, acyl cyanide: Florisil) to give ketone **2** or acyl cyanide **4**. Recrystallization from hexane or dry CH_2Cl_2/hexane gave pure needles.

Methyl *trans*-2-Hexenoate (6):

To a mixture of 2-hydroxy-3-heptenenitrile (**3h**; 0.253 g, 2.02 mmol) and $RuCl_2(PPh_3)_3$ (0.096 g, 0.10 mmol) in dry CH_2Cl_2 (3.0 mL) was added a 0.80 M solution of *t*-BuOOH in dry benzene (5.1 mL, 4.1 mmol) dropwise at r.t. over a period of 6 h. After stirring overnight $NaHSO_3$ (0.5 g) was added to decompose excess *t*-BuOOH. A mixture of MeOH (2.0 mL) and Et_3N (0.210 g, 2.08 mmol) was added dropwise, and the mixture was stirred for 3 h. After filtration the solvent was removed under reduced pressure. The residue was subjected to column chromatography (silica gel, Et_2O/pentane, 1:1) to give **6** (0.220 g, 85%) as a pale yellow oil.

IR (neat): ν = 2970, 1735 (C=O), 1660, 1440, 1180, 985 cm^{-1}.

^{1}H NMR ($CDCl_3$/270 MHz): δ = 0.94 (t, J = 7.3 Hz, 3 H, H^6), 1.49 (qt, J = 7.3, 7.3 Hz, 2 H, H^5), 2.19 (tdd, J = 7.3, 6.8, 1.7 Hz, 2 H, H^4), 3.73 (s, 3 H, OCH_3), 5.83 (dt, J = 15.6, 1.7 Hz, 1 H, H^2), 6.98 (dt, J = 15.6 Hz, 6.8 Hz, 1 H, H^3).

***trans*-*N*-Butyl-2-Hexenamide (7):**

To a mixture of cyanohydrin **3h** (0.128 g, 1.02 mmol) and $RuCl_2(PPh_3)_3$ (0.048 g, 0.050 mmol) in dry benzene (1.5 mL) was added a 0.80 M solution of *t*-BuOOH in dry benzene (2.5 mL, 2.0 mmol) dropwise at r.t. over a period of 4 h. After stirring overnight $NaHSO_3$ (0.30 g) was added to decompose excess *t*-BuOOH. $BuNH_2$ (3.0 mL) was added dropwise, and the mixture was stirred for 1 h. After filtration the solvent was removed under reduced pressure. The residue was subjected to column chromatography (silica gel, Et_2O) to give **7** (0.134 g, 77%) as a pale yellow oil.

IR (neat): ν = 3300 (NH), 2970, 2940, 2880, 1675 (C=O), 1640, 1550, 980 cm^{-1}.

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.93 (t, J = 7.1 Hz, 6 H, Me), 1.29–1.56 (m, 6 H, CH_2), 2.15 (ddt, J = 7.1, 1.5, 7.3 Hz, 2 H, H^4), 3.31 (dt, J = 7.1, 6.8 Hz, 2 H, NCH_2), 5.64 (br 1 H, NH), 5.77 (dt, J = 15.4, 1.5 Hz, 1 H, H^2), 6.82 (dt, J = 15.4, 7.1 Hz, 1 H, H^3).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 166.2 (C=O), 144.4, 123.8, 39.3, 34.1, 31.7, 21.5, 20.1, 13.8, 13.7.

Selective *N*-Benzoylation of Aminoalcohols 10:

All reactions must be carried out in a well-ventilated hood because of generation of HCN.

To a stirred solution of amino alcohol **10** (3.0 mmol) in dry CH_2Cl_2 (5.0 mL) was added a solution of benzoyl cyanide (**4a**; 3.0 mmol) in dry CH_2Cl_2 (5.0 mL) dropwise at r.t. over a period of 3 h, and the mixture was stirred overnight. The mixture was poured into 10% aq NaOH and extracted with CH_2Cl_2 (3 × 10 mL). The aqueous layer was treated with antiformin (NaClO) to decompose the cyanide ion. The combined organic layers were evaported under reduced pressure and dried (Na_2SO_4). After filtration and evaporation, the residue was subjected to column chromatography (silica gel, Et_2O/MeOH, 10:1) to give *N*-acylated product **11**.

Selective Primary *N*-Benzoylation of Polyamines 12:

All reactions must be carried out in a well-ventilated hood because of generation of HCN.

To a stirred solution of polyamine **12** (3.0 mmol) in dry CH_2Cl_2 (20 mL) was added a solution of benzoyl cyanide (**4a**; 6.0 mmol) in dry CH_2Cl_2 (10 mL) dropwise at r.t. over a period of 3 h, and the mixture was stirred overnight. After the same workup described above separation by column chromatography (silica gel, Et_2O/MeOH, 10:1) gave primary *N*-acylated product **13**.

***trans*-Cinnamoyl Cyanide (15):**

trans-2-Hydroxy-4-phenyl-3-butenenitrile (**14**; 0.322 g, 2.02 mmol) was oxidized according to the procedure described above. Separa-

tion by column chromatography (Florisil, dry Et_2O) gave **15** (0.293 g, 92%) as a yellow solid; mp 112.5–113.0 °C.

MS (EI): m/z = 157 (M^+, 21), 130 (23), 129 (16), 104 (53), 103 (M^+–COCN, 53), 79 (79), 78 (34), 77 (33), 76 (34), 63 (37), 52 (100), 51 (79).

IR (Nujol): ν = 2225 (CN), 1655 (C=O), 1620, 1450, 1235, 1200, 980, 765 cm^{-1}.

^1H NMR ($CDCl_3$, 270 MHz): δ = 6.87 (d, J = 16.1 Hz, 1 H), 7.45–7.59 (m, 3 H, ArH), 7.65 (d, J = 6.1 Hz, 2 H, ArH_o), 8.02 (d, J = 16.1 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 167.5, 155.0, 133.1, 132.8, 129.5, 125.3, 112.4 (CN).

N^1,N^8-Bis(*trans*-cinnamoyl)spermidine (16) (Maytenine):
Maytenine **16** was prepared by the reaction of spermidine (0.218 g, 1.50 mmol) with **15** (0.472 g, 3.00 mmol) according to the method described above. Separation by column chromatography (silica gel, $CHCl_3$/MeOH, 2:1) gave **16** (0.558 g, 92%); mp 156–157 °C (Lit.[42c] 157 °C).

IR (Nujol): ν = 3285 (NH), 1655 (C=O), 1620, 1540, 1350, 1220, 1130, 975, 760 cm^{-1}.

^1H NMR ($CDCl_3$, 60 MHz): δ = 1.37–2.10 (m, 6 H), 1.83 (br, 1 H), 2.67 (dd, J = 5.5, 5.5 Hz, 4 H), 3.40 (t, J = 5.5 Hz, 4 H), 6.30 (d, J = 16 Hz, 2 H), 6.90 (br, 2 H), 7.00–7.53 (m, 10 H), 7.50 (d, J = 16 Hz, 2 H).

Ruthenium-Catalyzed Oxidation of 18 with *t*-BuOOH:
Cyanohydrin **18** (0.322 g, 2.02 mmol) was oxidized according to the procedure described above. Separation by column chromatography (Florisil, dry Et_2O/dry hexane, 1:4) gave 2,3-dibenzyloxybenzoyl cyanide (**19**; 0.559 g, 33%) as a yellow oil:

IR (neat): ν = 3050, 2990, 2950, 2230 (CN), 1665 (C=O), 1600, 1585, 1485, 1380, 1320, 1270, 1090, 1000, 750, 700 cm^{-1}.

^1H NMR ($CDCl_3$, 60 MHz): δ = 5.10 (s, 2 H, OCH_2), 5.23 (s, 2 H, OCH_2), 7.13–7.70 (m, 13 H, ArH).

Preparation of N^1,N^8-Bis(2,3-dibenzyloxybenzoyl)spermidine (20):
Amidoamine **20** was prepared by the reaction of spermidine (0.102 g, 0.702 mmol) with **19** (0.501 g, 1.46 mmol) according to the procedure described above. Separation by column chromatography (silica gel, $CHCl_3$/MeOH) gave **20** (0.476, 87%) as a yellow oil.

IR (neat): ν = 3375 (NH), 2925, 1655 (C=O), 1580, 1530, 1460, 1375, 1270, 970, 750, 690 cm^{-1}.

^1H NMR ($CDCl_3$, 60 MHz): δ = 0.96–1.93 (m, 7 H, CCH_2C + NH), 1.93–2.85 (m, 4 H, CH_2N), 2.85–3.72 (m, 4 H, CH_2NCO), 5.00 (s, 4 H, OCH_2), 5.05 (s, 4 H, OCH_2), 6.72–7.77 (m, 28 H, ArH + CONH).

Preparation of N^1,N^8-Bis(2,3-dihydroxybenzoyl)spermidine (17):
A solution of **20** (0.476 g, 0.612 mmol), 5% Pd–C (0.100 g), and AcOH (0.5 mL) in abs. MeOH (5.0 mL) was stirred for 22 h at r.t. under H_2 atmosphere. After filtration the solvent was removed under reduced pressure to give **17** (0.243 g, 95%).

IR (Nujol): ν = 3350 (OH), 1670 (C=O), 1600, 1560, 1480, 1290, 1080, 775, 710 cm^{-1}.

^1H NMR ($CDCl_3$, 60 MHz): δ = 1.27–2.00 (m, 7 H, CCH_2C + NH), 2.67 (dt, J = 6.5, 6.5 Hz, 4 H, CH_2N), 3.07–3.67 (m, 4 H, CH_2NCO), 4.33–5.83 (br, 4 H, OH), 6.60–7.45 (m, 8 H, ArH + CONH).

3,7,11,19,23,27-Hexaazatricyclo[27.3.1.1^{13,17}]tetratriaconta-1(32), 13,15,17(34),29(33),30-hexaene-2,12,18,28-tetraone Hydrochloride (21 · 2HCl); Typical Procedure:
All reactions must be carried out in a well-ventilated hood because of generation of HCN.

To a stirred solution of 3,3′-diaminodipropylamine (0.326 g, 2.5 mmol) in dry MeCN (100 mL) was added a solution of isophthaloyl cyanide (0.460 g, 2.5 mmol) in dry MeCN (20 mL) dropwise at r.t. over a period of 15 min. After stirring overnight the solvent was removed under reduced pressure. The HCN generated was trapped with aq NaOH and then treated with NaClO. The residue was diluted with a mixture of MeOH (100 mL) and 2N HCl (5 mL). After stirring for 1 h, the solvent was removed under reduced pressure. The residual solid was purified by MPLC (ODS, MeOH/H_2O, 1:20) to give **21** · 2HCl as a colorless solid (0.343 g, 46%); mp 240–242 °C (dec.).

IR (KBr): ν = 3285, 2959, 2813, 1645 (C=O), 1545, 1451, 1325, 1306, 1225, 1188, 1123, 816, 704 cm^{-1}.

^1H NMR (D_2O, 500 MHz): δ = 2.11 (tt, J = 6.3, 7.6 Hz, 8 H, $NCH_2CH_2CH_2N$), 3.23 (t, J = 7.6 Hz, 8 H, NCH_2), 3.61 (t, J = 6.3 Hz, 8 H, $CONCH_2$), 7.57 (t, J = 7.8 Hz, 2 H), 7.93 (dd, J = 7.8, 1.6 Hz, 4 H), 8.11 (t, J = 1.6 Hz, 2 H).

^{13}C NMR (D_2O, 125.8 MHz): δ = 172.5 (C=O), 136.3, 133.2, 132.1, 128.6, 47.8, 39.4, 28.4.

21: MS (FD): m/z = 523 (M^+ + 1).

HRMS: m/z, $C_{28}H_{38}N_6O_4$ calc.: 522.2954; found: 522.2955.

3,7,11,18,22,26-Hexaazatricyclo[26.2.2.2^{13,16}]tetratriaconta-1(31), 13,15,28(32),29,33-hexaene-2,12,17,27-tetraone Hydrochloride (22 · 2HCl): 42% yield; mp 178–183 °C (dec).

IR (KBr): ν = 3063, 2960, 2793, 1628 (C=O), 1547, 1499, 1433, 1358, 1323, 1292, 1217, 1167, 1116, 1076, 1019, 1000, 981, 862, 689 cm^{-1}.

^1H NMR (D_2O, 500 MHz): δ = 2.09 (tt, J = 7.2, 6.1 Hz, 8 H, NCH_2CH_2), 3.15 (t, J = 7.2 Hz, 8 H, NCH_2), 3.63 (t, J = 6.1 Hz, 8 H, NCH_2), 7.74 (s, 8 H, ArH).

^{13}C NMR (D_2O, 125.8 MHz): δ = 173.2 (C=O), 139.3, 130.4, 47.8, 38.9, 28.6.

HRMS: m/z, $C_{28}H_{38}N_6O_4$ calc.: 522.2954; found: 522.2964.

3,7,12,16,24,28,33,37-Octaazatricyclo[37.3.1.1^{18,22}]tetratetraconta-1(42),18,20,22(44),39(43),40-hexaene-2,17,23,38-tetraone Hydrochloride (23 · 4HCl):

51% yield; mp 222–225 °C (dec).

IR (KBr): ν = 3264, 2957, 2766, 2475, 1640 (C=O), 1626, 1607, 1595, 1581, 1547, 1534, 1473, 1458, 1443, 1364, 1323, 1285, 1251, 1194, 1147, 1080, 1034, 887, 822, 765, 739, 693 cm^{-1}.

^1H NMR (D_2O, 500 MHz): δ = 1.91 (tt, J = 3.1, 7.6 Hz, 8 H, $NCH_2CH_2CH_2CH_2N$), 2.09 (tt, J = 3.1, 6.0 Hz, 8 H, $NCH_2CH_2CH_2N$), 3.21–3.24 (m, 16 H), 3.60–3.62 (m, 8 H), 7.69 (dd, J = 7.8, 7.8 Hz, 2 H), 7.96 (dd, J = 7.8, 1.6 Hz, 4 H), 8.08 (dd, J = 1.6, 1.6 Hz, 2 H).

^{13}C NMR (D_2O, 125.8 MHz): δ = 173.7 (C=O), 136.8, 133.3, 132.6, 129.5, 49.7, 47.7, 39.4, 28.2, 25.3.

MS (FD): m/z = 666 (M^+ + 1).

HRMS: m/z, $C_{36}H_{56}N_8O_4$ calc.: 664.4424; found: 664.4428.

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