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Enantioselective Alkylation of Hydrophobic Vitamin B_{12} Bearing a Binaphthyl Moiety

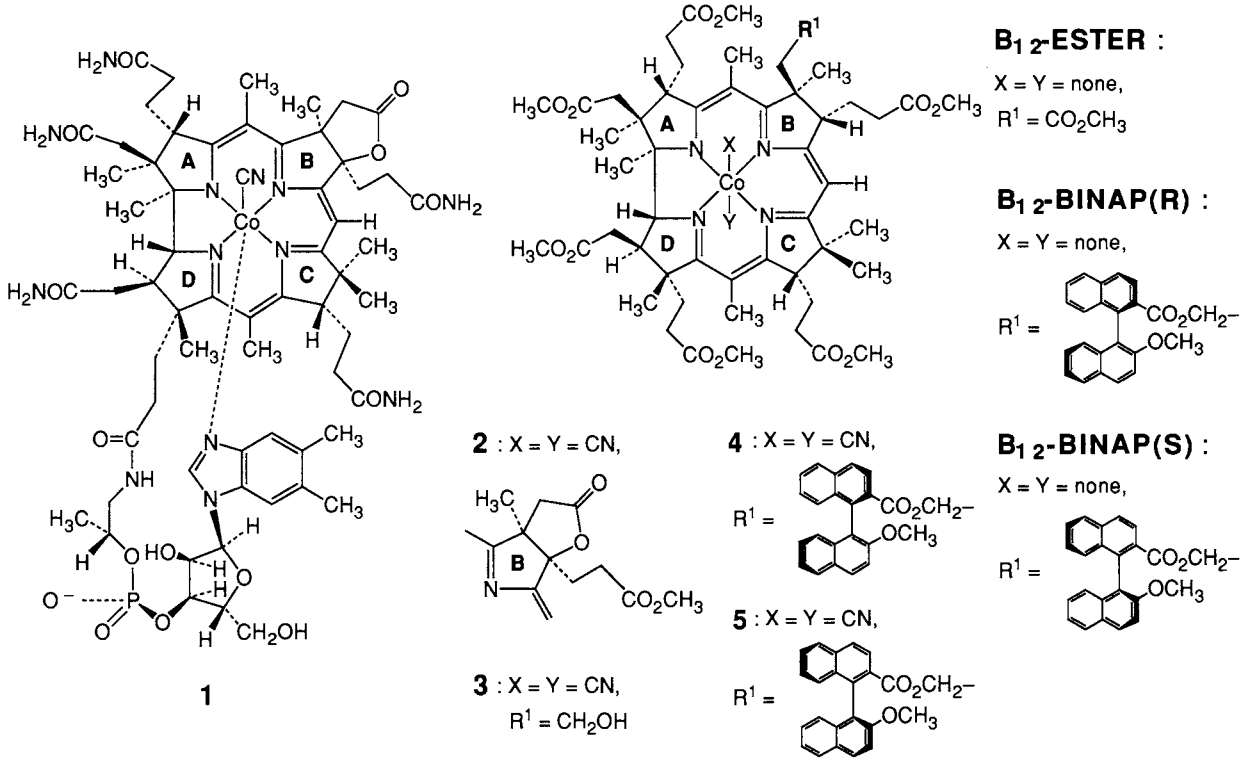
Yukito MURAKAMI,* Yoshio HISAEDA, Hiroshi KOHNO, and Teruhisa OHNO
Department of Chemical Science and Technology, Faculty of Engineering,
Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812

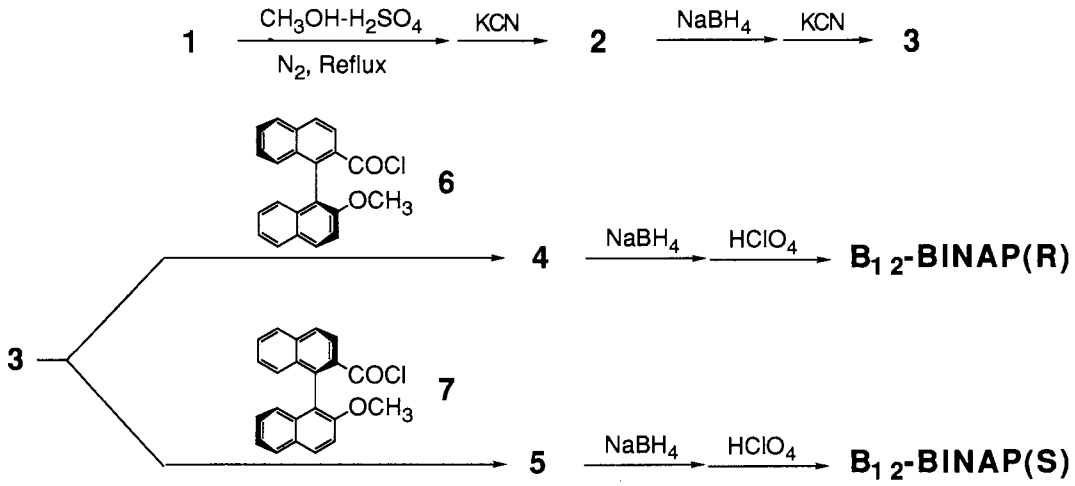
The enantioselective alkylation of hydrophobic vitamin B_{12} derivatives at the β-axial site was examined in methanol with various alkyl bromides, and those B_{12} analogues bearing a peripheral binaphthyl moiety showed the highest S-selectivity toward enantiomeric alkyl bromides among vitamin B_{12} models as caused by a steric effect of the peripheral substituent.

Vitamin B_{12} derivatives and model compounds have been found to catalyze the reduction of alkyl halides, nitriles, α,β-unsaturated carbonyl derivatives, and olefins.[1] These reactions proceed via formation of intermediates involving a Co–C bond that is subsequently cleaved and transformed into a C–H bond. On the other hand, one of the fascinating functions of naturally occurring vitamin B_{12} is referred to its potentiality as a chiral catalyst in asymmetric synthesis, since vitamin B_{12} creates a chiral reaction site provided by a corrin ring and peripheral substituents. However, such a structural framework does not achieve high enantioselectivity in nonenzymatic reactions.[2] In this regard, we report here preparation and enantioselective alkylation of novel vitamin B_{12} derivatives.

Hydrophobic vitamin B_{12} derivatives having a binaphthyl group placed at one of the peripheral sites were prepared by following the reaction steps shown in Scheme 1. Cyanocobalamin-c,8-lactone (**1**) was prepared by reaction of cyanocobalamin with *N*-bromosuccinimide.[3] Compound **2** was obtained by esterification of **1** after a method adopted for the synthesis of heptamethyl dicyanocobyrinate.[4] Compound **3** was derived from **2** by reduction with sodium tetrahydroborate, and purified by TLC on silica gel (Kiesel gel 60, Merck) with dichloromethane–methanol (95:5 v/v) containing 0.05%(w/w) potassium cyanide.

Compound **4**, having a binaphthyl group with R-configuration, was prepared by reaction of the acid chloride (**6**)[5] with **3** in the presence of triethylamine and 4-dimethylaminopyridine under nitrogen atmosphere, and purified by TLC on silica gel (Kiesel gel 60) with dichloromethane–methanol (94:6 v/v) containing 0.05%(w/w) potassium cyanide to give a purple powder: yield 67%; IR (KBr) 1760 (C=O ester) and 770 cm^{-1} (Ar-H); UV (methanol) 282, 369, 515, 526, and 588 nm; CD (methanol, 25.0 °C) 225.6 ($\Delta\varepsilon$ 107 deg cm^2 $dmol^{-1}$), 239.4 (–137), 284.5 (14.9), 305.6 (–5.7), 326.2 (3.9), 348.5 (–8.8), 395.5 (14.4), and 580.6 nm (–0.83). Found: C, 64.60; H, 6.18; N, 5.87%. Calcd for $C_{75}H_{87}CoN_6O_{16}$: C, 64.93; H, 6.32; N, 6.06%. Compound **5** having a binaphthyl group with S-configuration was obtained after the procedure employed for the preparation of **4**.





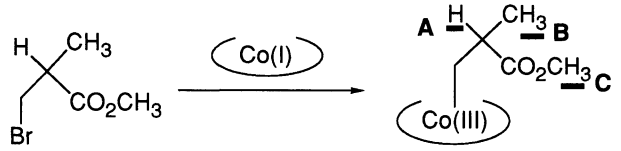
Scheme 1.

B_{12}-BINAP(R) was prepared from **4** in a manner similar to that applied to the synthesis of B_{12}-ESTER:[6] a brown powder, yield 68%; IR (KBr) 1730 (C=O ester) and 620 and 1100 cm^{-1} (ClO_4^-); UV (methanol) 266, 286, 298, 315, 400, and 468 nm. B_{12}-BINAP(S) was prepared after the method identical to that employed for the synthesis of B_{12}-BINAP(R).

Alkylated complexes were prepared by reactions of the hydrophobic vitamin B_{12} derivatives in the Co(I) state with various alkyl bromides in a manner as described previously,[7] and identified by electronic and ^{1}H-NMR spectroscopy.

The enantioselectivity in alkylation for the hydrophobic vitamin B_{12} derivatives was examined by 500 MHz ^{1}H-NMR spectroscopy, R-(+)-methyl 3-bromo-2-methylpropionate and S-(-)-methyl 3-bromo-2-methylpropionate (both from Aldrich Chemical Co., U.S.A.) being adopted as reference substrates. The major protons of the reference alkyl moieties placed at the β-axial site of the hydrophobic vitamin B_{12} were assigned as listed in Table 1 (refer to Eq. 1). The result indicates that the proton signals for the alkyl moiety with R-configuration appear in upper field ranges relative to those for the alkyl moiety with S-configuration. The enantioselectivity in alkylation was evaluated from the ^{1}H-NMR signal areas by the aid of a NMR1^{TM} software (New Methods Research, Inc., U.S.A.) on a DEC 5000/200PX workstation. When the racemic alkyl bromide was used, the reactivity of the S-enantiomer in the alkylation prevails over that of the corresponding R-enantiomer. The enantioselectivity data for the formation of other alkylated complexes were evaluated by the identical method as summarized in Table 2.

The alkylation study reveals the following facts with respect to enantioselectivity (refer to Eq. 2 and Table 2). (i) B_{12}-ESTER affords the alkylated complexes by reaction with alkyl bromides in S-selectivity, and the selectivity is enhanced as the bulkiness of a R^2 group increases. (ii) The highest enantioselectivity was observed for the reaction of B_{12}-ESTER with an alkyl bromide bearing a cyclohexyl ester group, 55% e.e. (iii) The hydrophobic vitamin B_{12} derivatives having a binaphthyl group, B_{12}-BINAP(R) and B_{12}-BINAP(S), exhibit higher selectivity toward an S-alkyl bromide than the simple hydrophobic vitamin B_{12}, B_{12}-ESTER; for the reaction with an alkyl bromide bearing a benzyl ester group, 65% e.e. This is the highest selectivity in the alkylation so far observed for vitamin B_{12}-related compounds. However, both B_{12}-BINAP(R) and B_{12}-BINAP(S) having R- and S-binaphthyl groups, respectively, undergo substitution at the β-axial site with the S-enantiomer more preferably than the R-enantiomer. The results indicate that the stereoselectivity is apparently originated from a stereospecific arrangements of the bulky peripheral substituents of the hydrophobic vitamin B_{12} in the alkylation and not from the chiral nature of the specific peripheral substituent.

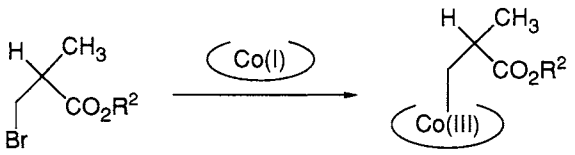


(1)

Table 1. Assignments of ^{1}H-NMR Signals for an Alkyl Moiety Placed at the Axial Site of B_{12}-ESTER in $CDCl_3$ at 25 °C

Assignment[a]	Splitting	δ/ppm[b] R-Configuration	δ/ppm[b] S-Configuration
A	Multiplet	−0.68	−0.50
B	Doublet	0.26	0.43
C	Singlet	3.35	3.40

a) Refer to Eq. 1. b) Tetramethylsilane as an internal reference.



(2)

Table 2. Enantioselectivity for the Reaction of Hydrophobic Vitamin B_{12} Derivatives with Various Alkyl Bromides in Methanol at Room Temperature[a)]

R^2 in alkyl bromide[b)]	Vitamin B_{12} derivative	Yield[c)]/%	% e.e.	(configuration)
CH_3	B_{12}-ESTER	67	34	(S)
C_2H_5	B_{12}-ESTER	63	44	(S)
C_4H_9	B_{12}-ESTER	79	44	(S)
C_8H_{17}	B_{12}-ESTER	60	51	(S)
$(CH_3)_3CH_2$	B_{12}-ESTER	66	45	(S)
Cyclohexyl	B_{12}-ESTER	86	55	(S)
$C_6H_5CH_2CH_2$	B_{12}-ESTER	66	47	(S)
$C_6H_5CH_2$	B_{12}-ESTER	68	49	(S)
$C_6H_5CH_2$	B_{12}-BINAP(R)	60	64	(S)
$C_6H_5CH_2$	B_{12}-BINAP(S)	54	65	(S)

a) Each reaction was carried out at a 1 : 50 molar ratio of a B_{12} derivative to an alkyl bromide; B_{12} derivative, 50 mg. b) Refer to Eq. 2. c) Isolated yield, purified by gel-filtration chromatography on Sephadex LH-20 with methanol as eluent in the dark; crude yield, above 80%.

In conclusion, the enantioselectivity in alkylation of the hydrophobic vitamin B_{12} having a binaphthyl group is superior to that of the simple hydrophobic vitamin B_{12}. This is originated from specific steric interactions between an alkyl moiety placed at the β-axial site and the peripheral substituents of hydrophobic vitamin B_{12} derivatives.

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