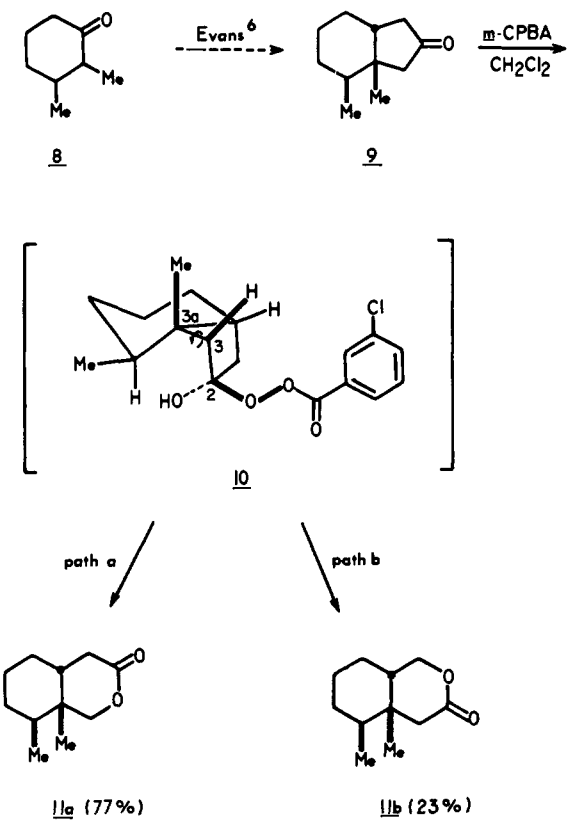
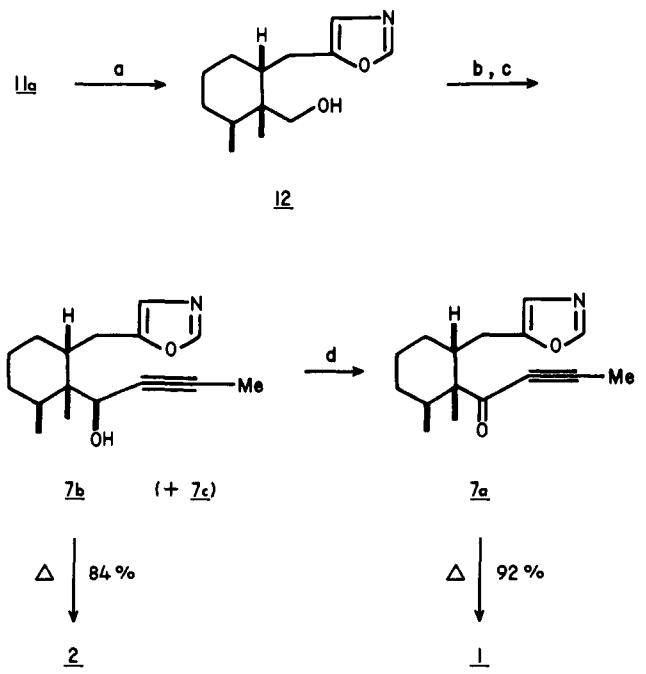
Scheme I



Scheme II[a]



[a] (a) $LiCH_2NC$, THF, DMF, 51% yield. (b) Me_2SO, $(COCl)_2$, 99% yield. (c) MeC≡CLi, THF, 69% yield. (d) Me_2SO, $(COCl)_2$, 98% yield.

of highly oxygenated sesquiterpenes will be the subject of future communications.

Acknowledgment. Financial support of this work by the National Science Foundation (Grant CHE-7800633) and the National Institutes of Health (Grant CA20483) is gratefully acknowledged. The Varian XL-200 spectrometer used in this work was financed in part by the National Science Foundation (Grant CHE-7908593), the Dreyfus Foundation, and Wesleyan University. D.G.W. was the recipient of a Sigma Xi Grant in Aid of Research during the course of this work.

High Enantioselectivity in Reductions with a Chiral Bis(NADH) Model Compound

Masahiko Seki, Naomichi Baba, Jun'ichi Oda, and Yuzo Inouye*

Institute for Chemical Research, Kyoto University Uji, Kyoto, Japan

Received March 5, 1981

The stereospecificity in parallel with the remarkable rate enhancement under mild conditions which are available in enzyme reactions have attracted and prompted organic chemists interested in synthesis to simulate the enzymic stereospecificity apart from the rate acceleration.

In order to gain further insight into the detailed mechanism of the alcohol dehydrogenase catalyzed hydrogen transfer in vivo and also examine the potentiality of asymmetric reduction in nonenzymic synthesis, some simplified systems involving chiral 1,4-dihydronicotinamides as a coenzyme mimic have been devised, in which "biomimetic" asymmetric reductions have been developed with some measure of success.[1]

In the course of our studies on asymmetric reduction[1f-j] of activated carbonyls and carbon–carbon double bonds by the use of chiral 1,4-dihydronicotinamide (NAH) derivatives carrying polar groups in the chiral 3-carbamoyl moiety, we have found that one of the diastereotopic faces of dihydropyridine nucleus is specifically blocked in situ by the oxidized form NA through a charge-transfer interaction. This is further consolidated by the intermolecular chelation of intervening magnesium with the side chain hydroxyl groups of both nicotinamides, thus permitting an easier access of the substrate carbonyl to the unhindered face of dihydronicotinamide.[1g]

The exogenously orienting effect of the oxidized form which accumulated during the conversion was cogently supported by the stereochemical evidence[1g] and was in fact realized by the initial addition of the oxidized form NA as well as the external addition of either chiral or achiral aromatics capable of chelating and/or CT complexing.[1f]

On the basis of this rationale, it would be possible to effect the specific blockage of the dihydronicotinamide face more securely by means of an *intramolecular* device, eventually leading to much-improved asymmetric yields.

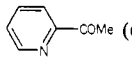
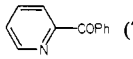
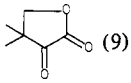
Thus designed and prepared are the novel chiral bis(NADH) model compounds whose intended C_2 symmetry constrains the equivalent dihydropyridine nuclei to block the specific face of each other. In principle, this constitutes another advantage of the bis compounds over the corresponding mono derivatives (C_1) in enantioselectivity.

In accord with the expectation, higher enantiomeric excess of the reduction products was obtained by the use of bis(NAH) **1**, **2**, and **3**[2] involving L-prolinamide as the chirality-inducing center,

(1) (a) A. Ohno, T. Kimura, S. Oka, and Y. Ohnishi, *Tetrahedron Lett.*, 757 (1978); (b) H. J. Ramesdonk, J. W. Verhoeven, U. K. Pandit, and Th. J. de Boer, *Rec. Trav. Chim. Pay-Bas*, **97**, 195 (1978); (c) T. Endo, H. Kawasaki, and M. Okawara, *Tetrahedron Lett.*, 23 (1979); (d) J. G. de Vries and R. M. Kellogg, *J. Am. Chem. Soc.*, **101**, 2759 (1979); (e) A. Ohno, M. Ikequchi, T. Kimura, and S. Oka, *Ibid.*, **101**, 7036 (1979); (f) T. Makino, T. Nunozawa, N. Baba, J. Oda, and Y. Inouye, *Tetrahedron Lett.*, 1683 (1979); (g) T. Makino, T. Nunozawa, N. Baba, J. Oda, and Y. Inouye, *J. Chem. Soc., Perkin Trans. 1*, 7, (1980); (h) N. Baba, T. Makino, J. Oda, and Y. Inouye, *Can. J. Chem.*, **58**, 387 (1980); (i) N. Baba, J. Oda, and Y. Inouye, *J. Chem. Soc., Chem. Commun.*, 815, (1980); (j) Y. Inouye, "Abstracts of Papers", Second Chemical Congress of the North American Continent at Las Vegas, Aug., 1980.

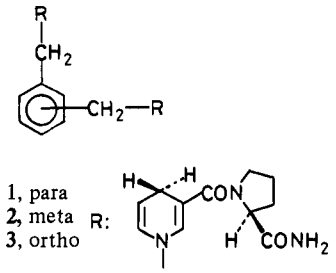
0002-7863/81/1503-4613$01.25/0

Table I. Reduction of Several Substrates with Chiral NAH Model Compounds

run[a]	NAH model	substrate	react temp, °C	react period, h	product: chem yield, %	product: $[\alpha]^{25}_D$, deg (c)	product: % ee	product: config	ref
1	1	$PhCOCO_2Et$ (4)	50	2	79.8	−97.6 (0.267[c])	93.5	R	6
2	1	4	room temp	1	66.6	−102.4 (1.75[c])	98.1	R	6
3	2	4	room temp	23	61.5	−35.4 (0.654[c])	34.0	R	6
4	3	4	room temp	23	69.5	−38.0 (0.621[c])	36.4	R	6
5	1	4	40	1	37.0	−23.2 (0.646[c])	18.4	R	6
6	1	$PhCOCF_3$ (5)	50	11	5.9	+6.6 (0.120[d])	49.5	S	7
7	1	 (6)	60	16.5	66.9	+50.8 (1.64[c])	89.7	R	8
8	1	 (7)	50	100	71.5	−123.3 (4.12[e])	i		9
9	1	$Ph(Me)C{=}C(CN)_2$ (8)	room temp	192	16.8	+4.1[f] (0.640[g])	23.2	R	10
10	1	 (9)	room temp	67	100[b]	−19.3 (0.150[h])	38.1	R	11

[a] All the reductions were run in a mixture of dry acetonitrile and dry chloroform (3:1 by volume) except run 5 where absolute ethanol was used as reaction medium. [b] Reaction conversion. [c] Dry ethanol. [d] Benzene. [e] Chloroform. [f] Optical rotation at 546 nm. [g] 95% ethanol. [h] Water. [i] α-Pyridylbenzyl alcohol obtained here showed, after the repeated careful purifications for enantiomeric integrity, the specific rotation by far higher than the recorded maximum value (±86.2°).

with substrate carbonyls **4**–**7**, **9** and carbon–carbon double bond in **8**. To our knowledge, the practically complete asymmetric induction attained here (Table I, run 2) with bis(NADH) model **1** is the highest recorded so far in this type of reduction.



The experimental procedure is exemplified by a typical run (Tabl I, run 2): the bis(NAH) **1** (904 mg, 1.66 mmol), magnesium perchlorate (371 mg, 1.66 mmol), and ethyl benzoylformate **4** (296 mg, 1.66 mmol) in a mixture of dry acetonitrile (600 mL) and dry chloroform (200 mL) were stirred at 25 °C in a nitrogen atmosphere for 1 h in the dark. After the usual workup,[1g] the reduction product ethyl (*R*)-mandelate was isolated pure in 66.6% (199 mg) chemical and 98.1% $[\alpha]^{25}_D$ −102.4° (*c* 1.75, EtOH), optical yields. The aqueous layer resulting from the workup was submitted to the modified sodium hydrosulfite reduction[2] to regenerate bis(NAH) **1** in a 42% recovery, which was recycled for further reductions to reproduce the same level of asymmetric induction.

As can be seen from the tabulated data, other substrates **5**–**9** when reduced with bis(NAH) derivatives carrying the same chiral center afforded the corresponding products of *R* configuration, except for 1-phenyl-2,2,2-trifluoroethanol with *S* configuration, in various chemical and optical yields, in which the reaction conditions were not optimized for individual runs.

The stereochemical outcome cogently supports the view[3] that the specific blockage of the diastereotopic face of NAH is at least one of the prime considerations in designing a highly effective NADH reductant. The stereochemical requirements for this specific blockage and therefore higher enantioselectivity were fulfilled by the molecular architecture of *p*-xylene-bridged bis(NAH) **1** which showed practically complete enantioselectivity in contrast to the poor performance of the ortho and meta congeners.

Dependence of the chemical and optical yields on magnesium was shown by an experiment in which ethyl benzoylformate was reduced with **1** in the presence of varying amount of magnesium. Thus the maximum enantiomeric excess was attained at 1:1 $Mg(ClO_4)_2$/bis(NAH) and remained constant thereafter. Of even more importance is the finding that the enantiomeric excess does not alter at all with reaction conversion. This is in striking contrast with our previous observation[1i] in the reduction with mono-NAH derivatives where the oxidized form NA substantially affected the steric course of reduction by participating in the transition state. The observation in the present system shows that the bis(NAH) reduction is a kinetically controlled single process and the participation of the oxidized form in situ may be safely ruled out. Actually, the initial addition of the oxidized bis(NA) form of **1** to the standard system (run 2) did not affect the stereochemistry of the reduction as indicated by the observed constancy in the enantiomeric excess.

Upon addition of magnesium perchlorate to **1**, the carbonyl absorption band at 1680 cm^{-1} shifted to a lower frequency, whereas the C–N band at 1605 cm^{-1} shifted to a higher value. This obviously shows that magnesium ion complexes to the primary amide carbonyl oxygen[4] of prolinamide. Other information about the complexation was supplied from a UV study which showed the formation of a 1:1 complex between the bis(NAH) **1** and Mg ion as corroborated by the mole ratio method.[5] The spectral

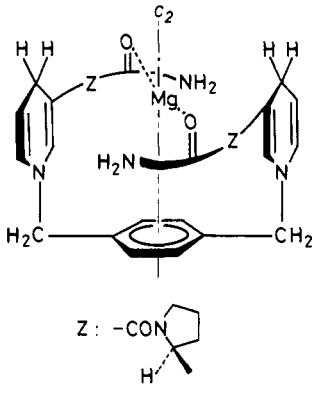
(2) The reductants **1**–**3** were prepared from the corresponding oxidized forms bis(NA) by the modified sodium hydrosulfite reduction: Sodium hydrosulfite (12.5 g) was added to a solution of the dinicotinium salts (1 g) in a carbon dioxide saturated solution of sodium bicarbonate (3 g in 50 mL of water), and the mixture was stirred vigorously. When foaming was extinguished, additional water (50 mL), anhydrous sodium carbonate (17.5 g), and chloroform (100 mL) were added and stirred for 5 h at ambient temperature in the dark. The chloroform layer containing the bis(NAH) was washed with water and dried over sodium sulfate, which was used as such for the reduction. UV, IR, ^1H, and ^{13}C NMR and TLC analyses fully substantiated the proposed structure at both the oxidized and the reduced forms: **1**: $[\alpha]^{25}_D$ −25.6° (*c* 2.03, $CHCl_3$); UV($CHCl_3$) 344 nm (ε 7.95 × 10^3). **2**: $[\alpha]^{25}_D$ −23.3° (*c* 4.35, $CHCl_3$); UV ($CHCl_3$) 348 nm (ε 7.67 × 10^3). **3**: $[\alpha]^{25}_D$ −72.0° (*c* 3.28, $CHCl_3$); UV ($CHCl_3$) 346 nm (ε 7.69 × 10^3).

(3) This is also supported by the high enantioselectivity found for the self-immolative asymmetric reduction with a 4-methyl-substituted dihydronicotinamide,[1e] irrespective of another chirality residing on the 3-carbamoyl side chain.

(4) (a) M. Hughes, R. H. Prince, and P. Wyeth, *J. Inorg. Nucl. Chem.*, **40**, 713 (1978). (b) M. Kanzaki, M. Nonoyama, and K. Yamazaki, *Kagaku*, **27**, 1182 (1972).
(5) J. H. Yoe and A. L. Jones, *Ind. Eng. Chem., Anal.* Ed., **16**, 111 (1944).
(6) R. Roger, *J. Chem. Soc.*, 2168 (1932).
(7) J. Jurczak, A. Konowal, and Z. Krawczyk, *Synthesis*, 258 (1977). H. M. Peters, D. M. Feigl, and H. S. Mosher, *J. Org. Chem.*, **33**, 4245 (1968).
(8) M. Imuta and H. Ziffer, *J. Org. Chem.*, **43**, 3530 (1978).
(9) A. G. Davies, J. Kenyon, and K. Thaker, *J. Chem. Soc.*, 3394 (1956).
(10) D. Cabaret and Z. Welvart, *J. Organomet. Chem.*, **80**, 199 (1974).

evidence, combined with the stereochemical outcome that the enantiomeric excess of the product mandelate was at a maximum by the use of equimolar bis(NAH) **1** and Mg, shows that the stereochemical requirements are accommodated well in the stoichiometric *intramolecular* chelation complex which exhibits the highest stereospecificity and is unaffected by an excess of metal ion.

It then seems likely that the operating bis(NAH) **1** assumes a C_2 conformation with the specific pro-*R* or pro-*S* hydrogens of the two juxtaposed equivalent dihydropyridine nuclei disposed outside and the C_2 axis passing through the interposing Mg and the center of the *p*-xylene bridge (**10**).



10

Acknowledgment. This work was supported in part by a grant in aid (521316) from the Ministry of Education of Japan for which we are deeply grateful.

(11) E. T. Stiller, S. A. Harris, J. Finkelstein, J. C. Keresztesy, and K. Folkers, *J. Am. Chem. Soc.*, **62**, 1785 (1940).

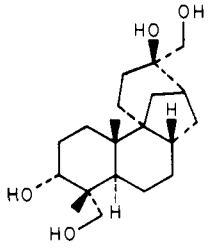
Total Synthesis of (±)-Maritimol

Eugene E. van Tamelen,* James G. Carlson,
Ronald K. Russell, and Steven R. Zawacky

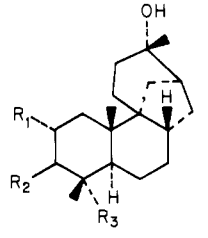
Department of Chemistry, Stanford University
Stanford, California 94305

Received April 20, 1981

Diterpenoids of the aphidicolane (**1**)–stemodane (**2**) type, including aphidicolin (**1**) as well as maritimol (**2a**) and other Stemodia components (**2b–d**), have attracted attention not only because of their novel structures but also because of certain biomedical and pharmacological properties.[1-4] We wish now to disclose the first maritimol (±) total synthesis, a stereospecific, nonrelay route which parallels in significant respects the probable biogenesis of this natural product.[5]

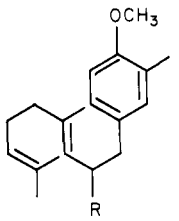


1

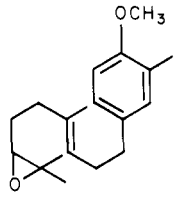


2a, R_1 = H; R_2 = OH; R_3 = CH_3
b, R_1 = R_2 = H; R_3 = CH_2OH
c, R_1 = OH; R_2 = H; R_3 = CH_3
d, R_1 = O; R_2 = H; R_3 = CH_3

Alkylation of phenylgeranyl thioether[6] anion (generated by the action of 1.1 equiv of *n*-C_4H_9Li on the thioether in THF at −78 °C) with 2-methyl-4-(chloromethyl)anisole[7] (1.1 equiv in THF at −78 °C) gave rise to the coupling product **3a** (85% after chromatography on SiO_2). Reductive desulfurization with Li



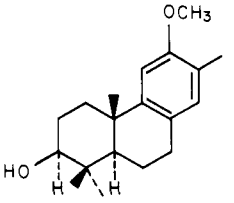
3a, R = SC_6H_5
b, R = H



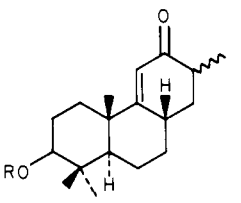
4

(3 equiv in NH_3 at −78 °C) generated (90%) polyene **3b** [bp 111 °C (0.03 mmHg)], which was converted via the terminal bromohydrin to the epoxide **4** (71% from **3b**)[8] (first 1.1 equiv of NBS in 5:1 THF–H_2O at 0 °C, then excess K_2CO_3 in CH_3OH at room temperature, followed by SiO_2 chromatography).

As a variant of the biocyclization process, Lewis acid treatment (BF_3·Et_2O or $SnCl_4$) of oxide **4** in aprotic solvent (CH_2Cl_2 or CH_3NO_2 at 0 °C; C_6H_6 at 25 °C) produced 25–50% hydrophenanthrene **5**,[9] initially as a clear gum but crystalline (mp 103–105 °C) after SiO_2 chromatography. In order to prepare



5



6a, R = H
b, R = $C_6H_5CH_2$

for the Diels–Alder reaction planned for construction of a fourth ring, the aromatic moiety in **5** was subjected to a Birch-type reduction (200 equiv of Li in 4:1:1 NH_3–THF–C_2H_5OH at reflux), generating, after hydrolysis (10:1 CH_3OH–7 N aqueous HCl at room temperature) of the intermediary enol ether, the conjugated enone **6a**, mp 55–57 °C (51% after SiO_2 chromatography).[10]

On successive exposure to $LiN[CH(CH_3)_2]_2$ (3.4 equiv in THF at 25 °C) and $(CH_3)_2$-*t*-C_4H_9SiCl (3.2 equiv in refluxing THF),

(1) Aphidicolin, a fungal metabolite with antiviral and antimitotic properties,[2] finds use as an inhibitor of DNA synthesis. Maritimol,[3] stemodinol (**2b**),[3] stemodinol (**2c**),[4] and stemodinone (**2d**)[4] occur in *stemodia maritima* L. (Scrophulariaceae), a plant used in the Caribbean for treatment of venereal disease.

(2) Brudret, K. M.; Dalziel, W.; Hesp, B.; Jarvis, J. A.; Neidle, S. *Chem. Commun.* **1972**, 1027.

(3) Hufford, C. D.; Guerrero, R. O.; Doorenbos, N. J. *J. Pharm. Sci.* **1976**, *65*, 778.

(4) Manchand, P. S.; White, J. D.; Wright, H.; Clardy, J. *J. Am. Chem. Soc.* **1973**, *95*, 2705.

(5) (a) For successful synthetic approaches to aphidicolin, see: Trost, B. M.; Nishimura, Y.; Yamamoto, K. *J. Am. Chem. Soc.* **1979**, *101*, 1328. McMurry, J. E.; Andrus, A.; Ksander, G. M.; Musser, J. H.; Johnson, M. A. *Ibid.* **1979**, *101*, 1330. (b) Total synthesis of (±)-aphidicolin: Corey, E. J.; Tius, M. A.; Das, J. *Ibid.* **1980**, *102*, 1742. (c) Total synthesis of (±)-stemodin (**2c**) and (±)-stemodinone (**2d**): Corey, E. J.; Tius, M. A.; Das, J. *Ibid.* **1980**, *102*, 7612.

(6) Altman, L. J.; Ash, L.; Marson, S. *Synthesis* **1974**, 129.

(7) Wenner, W. *J. Org. Chem.* **1951**, *16*, 457.

(8) IR 2959, 1495, 1250 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 1.18 (3 H, s), 1.22 (3 H, s), 1.58 (3 H, s) 2.15 (3 H, s), 2.30–2.70 (3 H, m), 3.78 (3 H, s), 4.90–5.40 (1 H, m), 6.45–6.95 (3 H, m).

(9) IR 3413, 2941, 1489, 1252, 1200, 1033, 733 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 0.90 (3 H, s), 1.08 (3 H, s), 1.22 (3 H, s), 2.16 (3 H, s), 2.20–2.37 (1 H, m), 2.73–2.90 (1 H, m), 3.24–3.40 (1 H, m), 3.80 (3 H, s), 6.71 (1 H, s), 6.82 (1 H, brs).

(10) IR 3450, 2940, 1670, 1605 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 0.87 (3 H, s), 1.03 (3 H, s), 1.08 (3 H, d, J = 6 Hz), 1.13 (3 H, s), 3.05–3.40 (1 H, m), 5.70–5.90 (1 H, m).

0002-7863/81/1503-4615$01.25/0