of the Schiff base of the D-amino amide. The filtrate (containing the L-amino acid) was concentrated in vacuo and applied to a Dowex 50 W ion-exchange column, which was eluted with 2 N NH_4OH. The ninhydrine positive fractions were collected and concentrated in vacuo. The resulting solid was washed with a 2-propanol/diethyl ether mixture to give (after drying in vacuo) 1.47 g (12.83 mmol, 95%) of L-allylglycine. $[\alpha]^{24}_D$ –42.7 (*c* 4, H_2O), $[\alpha]^{24}_D$ –6.6 (*c* 2, 5 N HCl).[28] Ee: 9.8 ± 1% (according to HPLC, using a Crownpack CR(+) column[19b]).

Enzymatic Resolution of 2-Amino-2-cyclopentyl-*N*-methoxyacetamide (36). A solution of **36** (3.01 g, 17.5 mmol) in water (60 mL) was adjusted to pH = 8.3 using NH_4OH. To the solution was added 2.5 g of a crude enzyme paste from *P. putida*. The resulting mixture was left at 37 °C for 22 h, after which the conversion was 43% (according to HPLC data, vide infra). The mixture was centrifuged at 10000 rpm for 15 min to remove the enzymes. Then benzaldehyde (1.35 mL, 1.41 g, 1.3 equiv relative to remaining starting material) was added and the solution was stirred for 1 h, during which time it became a white suspension due to the (selective) formation of the Schiff base of the remaining starting material. This suspension was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with water. The combined water layers were concentrated in vacuo, and the resulting residue was washed with acetone to give L-cyclopentylglycine (1.02 g, 98% based on 43% conversion) as a yellow solid. ^{1}H-NMR (200 MHz, D_2O/DCl): 3.61 (d, 1 H, *J* = 7.0 Hz, C*H*N), 2.34–2.17 (m, 1 H, CH_2CHCHN), 1.84–1.37 (m, 8 H, $-(CH_2)_4-$). Ee: (HPLC) 98%. The D-amino acid could be obtained as follows: to the combined organic layers was added 4 N HCl (50 mL) and the mixture was stirred for 17 h at rt (to effect cleavage of the Schiff base). After the layers were separated, the aqueous layer was refluxed for 24 h (to hydrolyze the *N*-methoxyamide). The solution was concentrated in vacuo, the residue (which contained the HCl salts of the D-amino acid and *O*-methylhydroxylamine) was dissolved in water (100 mL), and then Amberlyst 15 strongly acidic ion-exchange resin (20 g) was added. After 3 h of frequent swirling the mixture was filtered and washed several times with water until the water had a neutral pH. To the residue was then added NH_4OH (100 mL). After 1 h of frequent swirling the mixture was again filtered and washed with water until neutral pH. The filtrate (which now contained the free D-amino acid and free *O*-methylhydroxylamine) was decolorized by treatment with activated charcoal and concentrated in vacuo to give D-cyclopentylglycine (0.89 g, 65% based on 43% conversion) as a white solid. ^{1}H-NMR: vide supra. Ee: (HPLC) 74%. Conversion = 100 × ee (substrate)/(ee (substrate) + ee (product))% = 74/(74 + 98) = 43%.

Enzymatic Resolution of Valine *N*-Methoxyamide (42). Starting from 4 g of **42**, the same procedure as described for **36** was applied. The reaction was stopped after 32% conversion (according to HPLC data, vide infra). The yield of L-valine was 1.02 g (99% based on 32% conversion). ^{1}H-NMR (200 MHz, D_2O/DCl): 3.59 (d, 1 H, *J* = 4.2 Hz, C*H*N), 2.31–2.18 (m, 1 H, $(CH_3)_2CH$), 1.02 (d, 3 H, *J* = 7.2 Hz, CH_3CH), 0.97 (d, 3 H, *J* = 7.0 Hz, CH_3CH). Ee: (HPLC) 98%. The yield of D-valine was 1.69 g (82% based on 32% conversion). ^{1}H-NMR: vide supra. Ee: (HPLC) 46%. Conversion = 46/(46 + 98) = 32%.

Enzymatic Resolution of 2-Amino-*N*-methoxy-4-pentenamide (40). Starting from 0.98 g of **40**, the same procedure as described for **36** was applied (both the free amine and the formate salt of **40** can be used as the starting material). The reaction was stopped after 17 h, and after workup 0.16 g (21% of maximum total yield) of L-allylglycine was obtained as a yellow solid. ^{1}H-NMR (200 MHz, D_2O/DCl): 5.86–5.69 (m, 1 H, $-CH{=}CH_2$), 5.33–5.25 (m, 2 H, $-CH{=}CH_2$), 3.82 (m, 1 H, C*H*N), 2.60 (m, 2 H, $CH_2CH{=}$). $[\alpha]^{26}_D$ –4.3 (*c* 0.5, 1 N HCl) (lit.[19a] $[\alpha]^{25}_D$ –4.4 (*c* 0.5, 1 N HCl)). The remaining *N*-methoxyamide was not isolated because of the low conversion.

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Supplementary Material Available: ^{13}C NMR spectra for compounds **10, 11, 20–23, 28–30** and **34–37** and ^{1}H NMR spectra for compounds **26** and **31** (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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A Peptide–Aluminum Complex as a Novel Chiral Lewis Acid. Asymmetric Addition of Cyanotrimethylsilane to Aldehydes

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The enantioselective addition of cyanotrimethylsilane (TMSCN) to aldehydes promoted by the addition of a stoichiometric or catalytic amount of organoaluminum complexes of dipeptide esters or α-amino acid amides whose amino terminals are modified by a variety of protective groups is described. The reaction of benzaldehyde with TMSCN in the presence of a stoichiometric or catalytic amount of the complex prepared from *N*-[(2-hydroxy-1-naphthyl)methylene]-(*S*)-valyl-(*S*)-phenylalanine methyl ester (**1a**) or *N*-[(2-hydroxy-1-naphthyl)-methylene]-(*S*)-valine cyclohexylamide (**2a**) and trimethylaluminum gives (*R*)-mandelonitrile in good yield with enantioselectivity as high as 71%. The reaction of cyclohexanecarbaldehyde in the presence of the aluminum complex of *N*-(1-methyl-2-acetyl-vinyl)-(*S*)-valine cyclohexylamide (**3b**) furnishes the corresponding (*R*)-cyanohydrin in 38% ee, and the reaction of 2,2-dimethylpropionaldehyde with the aluminum complex of *N*-(4-toluenesulfonyl)-(*S*)-valyl-(*S*)-phenylalanine methyl ester (**4a**) gives the corresponding (*S*)-cyanohydrin in 67% ee.

Introduction

The design of chiral Lewis acids as catalysts for a variety of asymmetric reactions of carbonyl and related compounds has attracted much interest in synthetic organic chemistry. Derivatives of tartaric acid, binaphthyl, and oxazoline have been successfully used as chiral auxiliaries in the form of metal ligands, furnishing optically active molecules with high enantiopurities.[1] On the other hand, we recently demonstrated the utility of synthetic peptides

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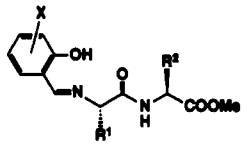
as chiral ligands for asymmetric synthesis, wherein a peptide–titanium complex anchored by salicylal type Schiff base 1 was found to give optically active cyanohydrins with



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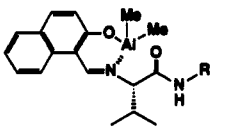
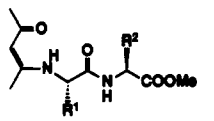
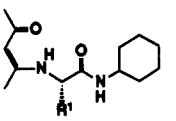


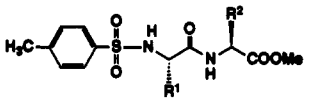
5: R = Bu^t, Cy



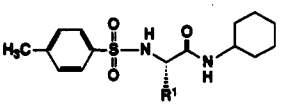
3a: R^1 = Pr^i (Val) R^2 = Bzl (Phe)



3b: R^1 = Pr^i (Val)



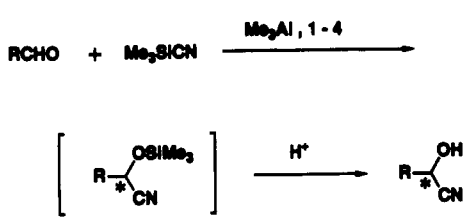
4a: R^1 = Pr^i (Val) R^2 = Bzl (Phe)

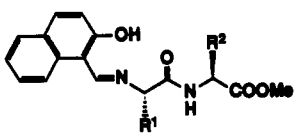


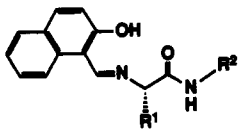
4b: R^1 = Pr^i (Val)

high enantioselectivities by the addition of HCN to aldehydes.[2,3] This result demonstrates that synthetic peptides can be practical chiral auxiliaries in asymmetric synthesis. The success of the asymmetric reaction catalyzed by the peptide–titanium complexes encouraged us to investigate the possibility of *using peptide–metal complexes as catalysts for Lewis acid promoted reactions.* The reaction we examined was asymmetric cyanosilylation by the addition of TMSCN to aldehydes, which was known to proceed in the presence of Lewis acid.[4,5] Cyanohydrins are recognized as versatile intermediates in synthetic organic chemistry since they can easily be converted to several other classes of compounds, such as α-hydroxy carboxylic acids and β-amino alcohols. In addition, the importance of optically active cyanohydrins has been dramatically demonstrated by their use as precursors to a pyrethroid insecticide[6] and as precursors to liquid crystalline materials.[7]

Scheme I







1a: R^1 = Pr^i (Val) R^2 = Bzl (Phe)
1b: = Pr^i (Val) = Ph (Phgly)
1c: = Pr^i (Val) = Pr^i (Val)
1d: = Bu^t (Leu) = Bu^t (Leu)
1e: = Bzl (Phe) = Bzl (Phe)

2a: R^1 = Pr^i (Val) R^2 = *cyclo*-hexyl
2b: = Bu^t (Leu) = *cyclo*-hexyl
2c: = Ph (Phgly) = *cyclo*-hexyl
2d: = Pr^i (Val) = Bu^t

Table I. Enantioselective Cyanosilylation of Benzaldehyde by the Complex of 1a with Metallic Reagents[a]

metallic reagent	time, h	yield, %[b]	% ee (confign)[c]
Me_3Al	102	41	61 (*R*)
Et_2AlCl	46	10	19 (*R*)
$TiCl_2(O^iPr)_2$	47	50	0
$Ti(O^iPr)_4$	125	80	19 (*R*)

[a] Reactions were carried out at −78 °C in toluene using 1.0 equiv of metallic reagent, 1.0 equiv of the peptide, and 3.0 equiv of TMSCN, based on the quantity of benzaldehyde. [b] Determined by ^{1}H NMR of a mixture of mandelonitrile and unreacted benzaldehyde. [c] Determined by ^{1}H NMR of menthyl carbonic ester of mandelonitrile.

In this paper, various peptides and α-amino acid amides whose N-terminals have been modified to 4-toluenesulfonyl (Ts),[8,9] 1-methyl-2-acetylvinyl (Acac), or (2-hydroxy-1-naphthyl)methylene (Nap) groups, to serve as ligands for chiral Lewis acid catalysts, are presented. Asymmetric cyanosilylations promoted by either a stoichiometric or catalytic amount of peptide–aluminum complex, prepared by treatment of these peptides with Me_3Al, are also described.[10]

Results and Discussion

The chiral ligand we chose to examine for the asymmetric cyanosilylation is an acyclic dipeptide ester in which

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Table II. Enantioselective Cyanosilylation of Benzaldehyde by the Complex of Dipeptide Esters or α-Amino Acid Amides with Me_3Al[a]

dipeptide ester or α-amino acid amide	time, h	yield, %	% ee (confign)
Nap-*S*-Val-*S*-Phe-OMe	102	41	61 (*R*)
Nap-*S*-Val-*S*-Phgly-OMe[b]	46	100	53 (*R*)
Nap-*S*-Val-*S*-Val-OMe	72	87	36 (*R*)
Nap-*S*-Leu-*S*-Leu-OMe	36	66	28 (*R*)
Nap-*S*-Phe-*S*-Phe-OMe	72	100	34 (*R*)
Nap-*S*-Val-NHCy[c]	5	66	71 (*R*)
Nap-*S*-Val-NHCy[d]	24	95[e]	69 (*R*)
Nap-*S*-Leu-NHCy	5	88	57 (*R*)
Nap-*S*-Phgly-NHCy	2	100	13 (*R*)

[a] Reaction conditions as in Table I. [b] Phgly: phenylglycine. [c] Cy: cyclohexyl. [d] 20 mol % of amide and of Me_3Al were used. [e] Isolated yield.

the amino group terminal of the peptide has been modified by the Schiff base of a salicylal derivative. Dipeptide ester **1a** composed of *S*-Val and *S*-Phe and bearing the (2-hydroxy-1-naphthyl)methylene group as part of the Schiff base moiety was employed, as the complex from **1a** and a titanium alkoxide has been proven as an effective chiral ligand for promoting the addition of HCN to aldehydes, resulting in asymmetric hydrocyanation.[2]

Several metallic reagents were examined as potential candidates to form a peptide–metal complex with **1a**, to serve as Lewis acid catalysts in the asymmetric cyanosilylation. The reaction was generally performed as follows (Scheme I): Complexation of the peptide with a metallic compound was carried out by mixing 1 equiv of the peptide and 1 equiv of a metallic compound at room temperature for 2 h in toluene to form a yellow solution. The solution was used directly for the asymmetric reaction, which was carried out by adding of 3 equiv of TMSCN followed by 1 equiv of aldehyde. During the reaction, consumption of the starting aldehyde was monitored by TLC. The reaction was terminated by the usual acidic workup to furnish the cyanohydrin, whose optical yield was determined by ^1H NMR and/or GC analysis of the corresponding menthyl carbonic[11] or 2-methoxy-2-(trifluoromethyl)phenylacetic acid (MTPA) ester.[12] The results of the asymmetric cyanosilylations of benzaldehyde by TMSCN with a stoichiometric amount of several peptide–metal complexes are summarized in Table I. Of the several metallic reagents used, Me_3Al was found to be the most effective. On the other hand, several reagents such as Et_2AlCl, $TiCl_2(O^iPr)_2$, and $Ti(O^iPr)_4$ did not promote asymmetric inductions to any significant extent. It is also interesting that the complex with $Ti(O^iPr)_4$, which showed high enantioselectivity in the hydrocyanation of aldehydes by the addition of HCN,[2] resulted in this case in considerably lower enantioselectivity (19% ee). On the other hand, the hydrocyanation of 3-$MeOC_6H_4CHO$ at −20 °C for 19 h using 10 mol % of the complex of Me_3Al was also ineffective (52% yield, 14% ee of *R*-isomer).[13] Thus, the catalyst systems of aluminum- and titanium–peptide complexes were found to be complementary with respect to cyanosilylation and hydrocyanation.

Table II summarizes the asymmetric cyanosilylation reaction of benzaldehyde using peptide–aluminum complexes of a variety of peptides and α-amino acid amides with Me_3Al. When the peptide **1a** composed of *S*-Val and *S*-Phe was used, (*R*)-cyanohydrin was obtained with 61% ee. In addition, the use of (*S*)-valine cyclohexylamide in place of dipeptide esters was also found to be effective, giving 71% ee of the (*R*)-cyanohydrin. It should be pointed out that a cyanohydrin trimethylsilyl ether was the sole product as confirmed by TLC monitoring of the reaction mixture. The reaction proceeded in the presence of a catalytic amount (20 mol % per benzaldehyde) of the aluminum complex of Nap-*S*-Val-NHCy in 69% ee with a slightly slower reaction rate.

Table III. Enantioselective Cyanosilylation by the Complex of 2a with Me_3Al[a]

aldehyde	time, h	yield, %[b]	% ee (confign)[c]
2-MeC_6H_4CHO	3	75	58 (*R*)
3-$MeOC_6H_4CHO$	4	92	56 (*R*)
cyclo-$C_6H_{11}CHO$	0.5	86	56 (*R*)
cyclo-$C_6H_{11}CHO$	17	61	56 (*R*)[d]
$C_6H_{13}CHO$	24	84	37 (*R*)[d]

[a] Reaction conditions as in Table I. [b] Isolated yield. [c] Enantiomeric excess in the case of aromatic aldehydes was determined by ^1H NMR of menthyl carbonic ester of the corresponding cyanohydrin, and that in the case of aliphatic aldehydes was determined by GC of MTPA ester of the corresponding cyanohydrin. [d] 10 mol % of amide and of Me_3Al were used.

The asymmetric cyanosilylations of several aldehydes in the presence of the aluminum complex of Nap-*S*-Val-NHCy are summarized in Table III. Aromatic aldehydes such as 2-MeC_6H_4CHO and 3-$MeOC_6H_4CHO$ afforded the corresponding cyanohydrins in 58% ee and 56% ee, respectively. The cyanosilylations of aliphatic aldehydes proceeded more rapidly than those of aromatic aldehydes. The reactions conducted with 10 mol % of the catalyst also afforded the cyanohydrins with moderate enantioselectivities.

In order to obtain information concerning the structures of the peptide–aluminum complexes in the asymmetric cyanosilylation reaction, ^1H NMR analysis of the mixture of equimolar amounts of Nap-*S*-Val-NH^{t}Bu (**2d**) and Me_3Al was carried out. The mixture was prepared by mixing **2d** with Me_3Al in C_6D_6 at 25 °C for 9 h. The spectrum revealed the disappearance of the phenolic hydroxyl proton at 14.96 ppm, the presence of the NH proton of the amide group (5.65 ppm), and two different singlet signals corresponding to the methyl groups bound to aluminum (0.09 and −0.25 ppm). Therefore, the structure of the peptide–aluminum complex was formulated as a dimethylaluminum phenoxide as shown in **5**. Nap-*S*-Val-NHCy (**2a**) was also found to react with Me_3Al to give the complex with a structure similar to that of **5**.

Asymmetric cyanosilylations using peptide–aluminum complexes anchored by a variety of protective groups at the N-termianl were also examined. The 1-methyl-2-acetylvinyl (Acac) group, which is assumed to form a similar chelating structure with (2-hydroxy-1-naphthyl)-methylene derivatives, was one of the groups used as an anchor. When Acac-*S*-Val-*S*-Phe-OMe (**3a**) was used, the ee value of the cyanohydrin was 27% (*R*) (52 h, 58% yield) in the reaction of cyclo-$C_6H_{11}CHO$ with TMSCN at −20 °C. In the case of Acac-*S*-Val-NHCy (**3b**), the enantiopurity was 38% (*R*) (45 h, 52% yield). However, peptides with other protective groups such as *tert*-butoxycarbonyl, (fluorenylmethoxy)carbonyl, and benzyloxycarbonyl were largely unsuccessful in promoting asymmetric inductions (less than 10% ee).

In addition, we examined the *p*-toluenesulfonyl group as an anchor for a peptide–aluminum complex (**4**, Table IV). Complexation of Ts-*S*-Val-S-Phe-OMe (**4a**) with Me_3Al at room temperature for 2 h followed by the cyanosilylation of cyclo-$C_6H_{11}CHO$ by TMSCN furnished the

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Table IV. Enantioselective Cyanosilylation by the Complex of 4 with Me_3Al[a]

peptide	aldehyde	time, h	yield, %[b]	% ee (confign)[c]
Ts-*S*-Val-*S*-Phe-OMe	cyclo-$C_6H_{11}CHO$	35	78	26 (*S*)
	$C_6H_{13}CHO$	17	47	18 (*S*)
	$(CH_3)_3CCHO$	18	83	67 (*S*)
Ts-*S*-Val-NHCy	cyclo-$C_6H_{11}CHO$	4	55	2 (*S*)

[a] Reaction conditions as in Table I. Reactions were carried out at −20 °C. The complexation of 4 with Me_3Al was performed at 110 °C for 2 h. [b] Isolated yield. [c] Determined by GC of MTPA ester of the corresponding cyanohydrin.

corresponding cyanohydrin in 4% ee (*R*). In contrast, when the complexation of **4a** with Me_3Al was performed at 110 °C for 2 h, the cyanohydrin of cyclo-$C_6H_{11}CHO$ was afforded in 26% ee (*S*), with a stereochemical preference opposite to that observed with **2a** and **3a**. The reaction with 2,2-dimethylpropionaldehyde as substrate proceeded fairly selectively to give the (*S*)-cyanohydrin of 67% ee.

Conclusion

Acyclic dipeptide esters and α-amino acid amides in which the N-terminal has been modified by the (2-hydroxy-1-naphthyl)methylene Schiff base (Nap), 1-methyl-2-acetylvinyl (Acac), or *p*-toluenesulfonyl group (Ts) were found to be efficient chiral auxiliaries in asymmetric cyanosilylation catalyzed by their complexes with Me_3Al.

Experimental Section

General. Melting points are uncorrected. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane (δ = 0). GC analyses were performed using a flame ionization detector and a capillary column (CBP20-M25-025). Thin-layer chromatography (TLC) was performed on Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.25 mm). Column chromatography was carried out on silica gel 60 (Merck, 70–230 mesh).

Toluene, THF, and benzene-d_6 were distilled from sodium benzophenone ketyl under N_2. Methylene chloride, TMSCN, and aldehydes were distilled from CaH_2. Me_3Al was distilled under N_2 and used as a 1 M solution in toluene. Other chemicals were purchased and used as such.

Preparation of Dipeptides Esters. *N*-[(2-Hydroxy-1-naphthyl)methylene]-(*S*)-valyl-(*S*)-phenylalanine Methyl Ester (Nap-*S*-Val-*S*-Phe-OMe, 1a). Z-*S*-Val-*S*-Phe-OMe was synthesized by the procedure described previously[5a] and used for the following reaction without further purification.

To a solution of 3.5 g (8.5 mmol) of (benzyloxycarbonyl)-*S*-valyl-*S*-phenylalanine methyl ester in 300 mL of MeOH was added 200 mg of palladium–carbon (5%) and the suspension was stirred for 5 h under H_2. The suspension was filtered, and to the filtrate was added 2.2 g (12.8 mmol) of 2-hydroxy-1-naphthaldehyde, and the solution was stirred for 5 h. The resulting yellow suspension was concentrated and the yellow solid was washed with Et_2O and dried in vacuo to give 2.7 g (64%) of Nap-*S*-Val-*S*-Phe-OMe, which was recrystallized from MeOH: mp 216.1–217.9 °C; $[\alpha]^{26}_D$ −28.2° (*c* 1.00, dioxane); IR (KBr) 3460 (br), 2970, 1740, 1660, 1625, 1170, 740 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 14.38 (br s, 1 H), 9.05 (s, 1 H), 8.02 (d, *J* = 8.1 Hz, 1 H), 7.84 (d, *J* = 9.4, Hz, 1 H), 7.75 (d, *J* = 7.3 Hz, 1 H), 7.49–7.55 (m, 1 H), 7.32–7.38 (m, 1 H), 7.13–7.28 (m, 6 H), 6.42 (br d, *J* = 7.7 Hz, 1 H), 4.86–4.93 (m, 1 H), 3.73 (d, *J* = 4.3 Hz, 1 H), 3.68 (s, 3 H), 3.20 ($^1/_2$ AB qd, *J* = 13.7, 5.6 Hz, 1 H), 3.05 ($^1/_2$ AB qd, *J* = 13.7, 7.7 Hz, 1 H), 2.39–2.51 (m, 1 H), 0.88 (d, *J* = 6.8 Hz, 3 H), 0.82 (d, *J* = 6.8 Hz, 3 H). Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 72.08; H, 6.48; N, 6.40.

Preparation of other peptides and amides bearing Schiff base (**1b–e, 2a–d**) were performed similarly to the above or following the procedure as described in the literature with slight modification.[14]

***N*-[(2-Hydroxy-1-naphthyl)methylene]-(*S*)-valyl-(*S*)-phenylglycine methyl ester (Nap-*S*-Val-*S*-Phgly-OMe, 1b):** mp 191.8–192.5 °C; $[\alpha]^{26}_D$ +31.1° (*c* 0.93, $CHCl_3$); IR (KBr) 3460 (br), 2970, 1740, 1665, 1630, 1540, 1210, 740 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 14.52 (br s, 1 H), 9.13 (s, 1 H), 8.06 (d, *J* = 8.1 Hz, 1 H), 7.84 (d, *J* = 9.0 Hz, 1 H), 7.76 (d, *J* = 6.8 Hz, 1 H), 7.51–7.57 (m, 1 H), 7.32–7.39 (m, 6 H), 7.17 (d, *J* = 9.0 Hz, 1 H), 7.12 (br d, *J* = 6.8 Hz, 1 H), 5.61 (d, *J* = 6.8 Hz, 1 H), 3.87 (d, *J* = 4.3 Hz, 1 H), 3.68 (s, 3 H), 2.42–2.55 (m, 1 H), 0.93 (d, *J* = 6.8 Hz, 6 H). Anal. Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69. Found: C, 71.62; H, 6.24; N, 6.72.

***N*-[(2-Hydroxy-1-naphthyl)methylene]-(*S*)-valyl-(*S*)-valine methyl ester (Nap-*S*-Val-*S*-Val-OMe, 1c):** mp 247.5–248.0 °C; $[\alpha]^{26}_D$ +89.7° (*c* 0.30, $CHCl_3$); IR (KBr) 3460 (br), 2970, 1740, 1665, 1630, 1215, 740 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 14.57 (br s, 1 H), 9.13 (s, 1 H), 8.07 (d, *J* = 8.6 Hz, 1 H), 7.84 (d, *J* = 9.0 Hz, 1 H), 7.76 (d, *J* = 8.1 Hz, 1 H), 7.51–7.57 (m, 1 H), 7.33–7.39 (m, 1 H), 7.17 (d, *J* = 9.0 Hz, 1 H), 6.55 (br d, *J* = 6.8 Hz, 1 H), 4.60 (dd, *J* = 8.6, 4.7 Hz, 1 H), 3.88 (d, *J* = 3.9 Hz, 1 H), 3.67 (s, 3 H), 2.51–2.63 (m, 1 H), 2.17–2.29 (m, 1 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H). Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.36. Found: C, 68.43; H, 7.27; N, 7.36.

***N*-[(2-Hydroxy-1-naphthyl)methylene]-(*S*)-leucyl-(*S*)-leucine methyl ester (Nap-*S*-Leu-*S*-Leu-OMe, 1d):** mp 197.1–199.2 °C; $[\alpha]^{26}_D$ +19.1° (*c* 0.45, $CHCl_3$); IR (KBr) 3450 (br), 2970, 1740, 1680, 1625, 1195, 750 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 14.37 (s, 1 H), 9.14 (s, 1 H), 8.04 (d, *J* = 8.6 Hz, 1 H), 7.82 (d, *J* = 9.0 Hz, 1 H), 7.72 (d, *J* = 8.1 Hz, 1 H), 7.50–7.56 (m, 1 H), 7.32–7.38 (m, 1 H), 7.27 (d, *J* = 9.4 Hz, 1 H), 6.44 (d, *J* = 8.1, 1 H), 4.61–4.69 (m, 1 H), 4.09–4.14 (m, 1 H), 3.68 (s, 3 H), 1.80–1.99 (m, 2 H), 1.55–1.76 (m, 4 H), 0.94–0.98 (m, 12 H). Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79. Found: C, 69.64; H, 7.80; N, 6.69.

***N*-[(2-Hydroxy-1-naphthyl)methylene]-(*S*)-phenylalanyl-(*S*)-phenylalanine methyl ester (Nap-*S*-Phe-*S*-Phe-OMe, 1e):** mp 164.3–164.9 °C; $[\alpha]^{26}_D$ −51.1° (*c* 0.21, $CHCl_3$); IR (KBr) 3450 (br), 2950, 1735, 1660, 1620, 1180, 730 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 14.03 (br s, 1 H), 8.69 (s, 1 H), 7.81 (d, *J* = 9.0 Hz, 1 H), 7.70–7.74 (m, 2 H), 7.39–7.46 (m, 1 H), 7.12–7.37 (m, 10 H), 6.99–7.03 (m, 2 H), 6.48 (d, *J* = 8.1 Hz, 1 H), 4.87–4.94 (m, 1 H), 4.15 (dd, *J* = 9.0, 3.4 Hz, 1 H), 3.68 (s, 3 H), 3.39 ($^1/_2$ AB qd, *J* = 13.7, 3.4 Hz, 1 H), 3.09–3.11 (AB m, 2 H), 3.01 ($^1/_2$ AB qd, *J* = 13.7, 9.0 Hz, 1 H). Anal. Calcd for $C_{30}H_{28}N_2O_4$: C, 74.98; H, 5.87; N, 5.83. Found: C, 74.71; H, 5.84; N, 6.13.

***N*-[(2-Hydroxy-1-naphthyl)methylene]-(*S*)-valine cyclohexylamide (Nap-*S*-Val-NHCy, 2a):** mp 218.3–219.7 °C; $[\alpha]^{26}_D$ +67.7° (*c* 0.98, $CHCl_3$); IR (KBr) 3490 (br), 3060, 2940, 1660, 1635, 1540, 740, 720 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 14.60 (s, 1 H), 9.07 (s, 1 H), 8.05 (d, *J* = 8.6 Hz, 1 H), 7.83 (d, *J* = 9.0 Hz, 1 H), 7.75 (d, *J* = 8.1 Hz, 1 H), 7.51–7.57 (m, 1 H), 7.33–7.39 (m, 1 H), 7.13 (d, *J* = 9.4 Hz, 1 H), 5.95 (d, *J* = 8.1 Hz, 1 H), 3.79–3.87 (m, 1 H), 3.83 (d, *J* = 4.3 Hz, 1 H), 2.49–2.61 (m, 1 H), 1.57–1.97 (m, 6 H), 1.10–1.41 (m, 4 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 0.96 (d, *J* = 7.3 Hz, 3 H). Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 74.67; H, 8.06; N, 8.08.

***N*-[(2-Hydroxy-1-naphthyl)methylene]-(*S*)-leucine cyclohexylamide (Nap-*S*-Leu-NHCy, 2b):** mp 197.0–199.2 °C; $[\alpha]^{26}_D$ +51.4° (*c* 1.00, $CHCl_3$); IR (KBr) 3470 (br), 2940, 1660, 1630, 740 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 14.39 (s, 1 H), 9.05 (s, 1 H), 8.01 (d, *J* = 8.1 Hz, 1 H), 7.81 (d, *J* = 9.0 Hz, 1 H), 7.72 (d, *J* = 6.8 Hz, 1 H), 7.49–7.55 (m, 1 H), 7.31–7.37 (m, 1 H), 7.08 (d, *J* = 9.0 Hz, 1 H), 6.03 (d, *J* = 8.1 Hz, 1 H), 4.05 (dd, *J* = 9.0, 4.7 Hz, 1 H), 3.71–3.84 (m, 1 H), 1.08–1.95 (m, 13 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H). Anal. Calcd for $C_{23}H_{30}N_2O_2$: C, 75.38; H, 8.25; N, 7.64. Found: C, 74.99; H, 8.09; N, 7.38.

***N*-[(2-Hydroxy-1-naphthyl)methylene]-(*S*)-phenylglycine cyclohexylamide (Nap-*S*-Phgly-NHCy, 2c):** mp 200.0–202.5 °C dec; $[\alpha]^{26}_D$ +45.8° (*c* 1.00, $CHCl_3$); IR (KBr) 3450 (br), 2930, 1660, 1630, 745 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 14.55 (s, 1 H), 9.20 (s, 1 H), 8.00 (d, *J* = 8.6 Hz, 1 H), 7.81 (d, *J* = 9.0 Hz,

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1 H), 7.72 (d, J = 8.1 Hz, 1 H), 7.31–7.54 (m, 7 H), 7.11 (d, J = 9.4 Hz, 1 H), 6.06 (d, J = 7.3 Hz, 1 H), 5.15 (s, 1 H), 3.73–3.87 (m, 1 H), 1.53–1.94 (m, 6 H), 1.10–1.43 (m, 4 H). Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.65; H, 6.83; N, 7.21.

N-[(2-Hydroxy-1-naphthyl)methylene]-(S)-valine *tert*-butylamide (Nap-S-Val-NH^{t}Bu, 2d): mp 234.8–237.0 °C; $[\alpha]^{26}_D$ +112.7° (c 1.00, $CHCl_3$); IR (KBr) 3430 (br), 3060, 2960, 1660, 1620, 735 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 14.58 (s, 1 H), 9.06 (s, 1 H), 8.07 (d, J = 8.5 Hz, 1 H), 7.84 (d, J = 9.0 Hz, 1 H), 7.76 (d, J = 8.1 Hz, 1 H), 7.51–7.58 (m, 1 H), 7.33–7.39 (m, 1 H), 7.14 (d, J = 9.0 Hz, 1 H), 5.85 (s, 1 H), 3.73 (d, J = 4.3 Hz, 1 H), 2.47–2.62 (m, 1 H), 1.37 (s, 9 H), 1.03 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H). Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.46; H, 8.07; N, 8.41.

N-(1-Methyl-2-acetylvinyl)-(S)-valyl-(S)-phenylalanine Methyl Ester (Acac-S-Val-S-Phe-OMe, 3a). To a solution of 0.56 g (10 mmol) of KOH in a mixture of 25 mL of EtOH and 5 mL of MeOH were added 1.17 g (10 mmol) of (S)-valine and 1.0 mL (10 mmol) of 2,4-pentanedione, and the suspension was refluxed to dissolve the (S)-valine. The resulting solution was concentrated to give crude Acac-S-Val-OK quantitatively as a yellow solid, which was used for the following reaction without further purification.

To a precooled (0 °C) suspension of 0.48 g (2.0 mmol) of Acac-S-Val-OK in 5 mL of THF were added 0.26 mL (2.0 mmol) of isobutyl chloroformate and a precooled (0 °C) suspension of (S)-phenylalanine methyl ester (2.0 mmol) in 5 mL of THF, which was prepared by dehydrochlorination of (S)-phenylalanine methyl ester hydrochloride (0.43 g) with 0.28 mL (2.0 mmol) of Et_3N. The suspension was stirred for 1 h at 0 °C and overnight at room temperature. After the solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 and the solution was washed with saturated H_3BO_3 and saturated $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the crude product as a solid, which was purified by chromatography on silica gel (hexane/ethyl acetate = 5:1), after removal of the solvent, to afford 0.35 g (48%) of Acac-S-Val-S-Phe-OMe, which was recrystallized from ether: mp 125.0–127.0 °C; $[\alpha]^{26}_D$ +266.3° (c 1.00, $CHCl_3$); IR (KBr) 3500 (br), 2980, 1740, 1680, 1570, 1225, 745 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.97 (d, J = 8.1 Hz, 1 H), 7.14–7.24 (m, 3 H), 7.03 (d, J = 6.4 Hz, 2 H), 6.33 (d, J = 9.0 Hz, 1 H), 5.03 (s, 1 H), 4.76–4.84 (m, 1 H), 3.77 (dd, J = 8.3, 4.1 Hz, 1 H), 3.65 (s, 3 H), 2.90–3.11 (AB, 2 H), 2.19–2.30 (m, 1 H), 2.01 (s, 3 H), 1.78 (s, 3 H), 0.85 (d, J = 6.8 Hz, 3 H), 0.74 (d, J = 7.3 Hz, 3 H). Doublet signal at 10.97 ppm is assigned to NH of the enamine form (**3a**), but not OH of the corresponding enol form (HOC=CC=NC$_\alpha$). Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.63; H, 7.82; N, 7.80.

N-(1-Methyl-2-acetylvinyl)-(S)-valine Cyclohexylamide (Acac-S-Val-NHCy, 3b). **3b** was prepared in a manner similar to that of **3a**: mp 154.0–156.1 °C; $[\alpha]^{26}_D$ +371.6° (c 0.63, $CHCl_3$); IR (KBr) 3450 (br), 2930, 1655, 1580 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 11.07 (d, J = 8.1 Hz, 1 H), 5.92 (d, J = 7.3 Hz, 1 H), 5.14 (s, 1 H), 3.86 (dd, J = 8.5, 3.9 Hz, 1 H), 3.72–3.83 (m, 1 H), 2.37–2.49 (m, 1 H), 2.08 (s, 3 H), 1.87 (s, 3 H), 1.55–1.93 (m, 6 H), 1.06–1.44 (m, 4 H), 1.01 (d, J = 6.8 Hz, 3 H), 1.00 (d, J = 6.8 Hz, 3 H). Doublet signal at 11.07 ppm is assigned to NH of the enamine form (**3b**), but not OH of the corresponding enol form (HOC=CC=NC$_\alpha$). FAB-HRMS calcd for $C_{16}H_{29}N_2O_2$ (MH$^+$) m/z 281.2229, obsd 281.2240.

N-(p-Toluenesulfonyl)-(S)-valyl-(S)-phenylalanine Methyl Ester (Ts-S-Val-S-Phe-OMe, 4a). To a mixture of 0.54 g (2.0 mmol) of Ts-S-Val[9] in 8 mL of CH_2Cl_2, 0.43 g (2.0 mmol) of (S)-phenylalanine methyl ester hydrochloride, and 0.34 g (2.2 mmol) of 1-hydroxybenzotriazole was added 0.31 mL (2.2 mmol) of triethylamine. The solution was cooled to 0 °C, and 0.45 g (2.2 mmol) of DCC was added. The suspension was stirred for 1 h at 0 °C and overnight at room temperature.

The suspension was filtered in order to remove the resulting white solid which was washed with 10 mL of CH_2Cl_2 repeatedly. The filtrate was washed with 5% aqueous citric acid (30 mL), water (30 mL), 5% aqueous $NaHCO_3$ (30 mL), and water (30 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo to leave the crude product as a solid, which was purified by chromatography on silica gel (hexane/ethyl acetate = 2:1), after removal of the solvent, to afford 0.41 g of Ts-S-Val-S-Phe-OMe in 94% yield, which was recrystallized from Et_2O: mp 153.6–154.7 °C; $[\alpha]^{26}_D$ +73.8° (c 0.88, $CHCl_3$); IR (KBr) 3460 (br), 2950, 1740, 1640, 1535, 1360, 1200, 1155, 805 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.74 (d, J = 8.3 Hz, 2 H), 7.23–7.27 (m, 5 H), 6.93–6.96 (m, 2 H), 6.48 (d, J = 7.6 Hz, 1 H), 5.70 (d, J = 8.6 Hz, 1 H), 4.65–4.72 (m, 1 H), 3.65 (s, 3 H), 3.58 (dd, J = 8.6, 5.1 Hz, 1 H), 2.88 (AB, 2 H), 2.34 (s, 3 H), 1.90–2.07 (m, 1 H), 0.85 (d, J = 6.8 Hz, 3 H), 0.77 (d, J = 6.8 Hz, 3 H). Anal. Calcd for $C_{22}H_{28}N_2O_5S$: C, 61.09; H, 6.52; N, 6.48. Found: C, 61.09; H, 6.56; N, 6.48.

N-(p-Toluensulfonyl)-(S)-valine Cyclohexylamide (Ts-S-Val-NHCy, 4b). Compound **4b** was prepared in a manner similar to that of **4a**: mp 225.0–226.0 °C; $[\alpha]^{26}_D$ −2.4° (c 0.65, $CHCl_3$); IR (KBr) 3460 (br), 2930, 1640, 1555, 1160, 810 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.71 (d, J = 8.3 Hz, 2 H), 7.28 (d, J = 8.1 Hz, 2 H), 5.55 (d, J = 8.1 Hz, 1 H), 5.22 (d, J = 8.1 Hz, 1 H), 3.47–3.60 (m, 1 H), 3.36 (dd, J = 8.1, 5.1 Hz, 1 H), 2.40 (s, 3 H), 1.97–2.10 (m, 1 H), 1.53–1.81 (m, 6 H), 0.90–1.38 (m, 4 H), 0.85 (t, J = 7.0 Hz, 6 H). Anal. Calcd for $C_{18}H_{28}N_2O_3S$: C, 61.33; H, 8.01; N, 7.95. Found: C, 61.08; H, 7.76; N, 7.88.

General Procedure for Asymmetric Cyanosilylation of Aldehydes. Method A. To a suspension of 88 mg (0.25 mmol) of Nap-S-Val-NHCy in 4 mL of toluene was added 0.25 mL (0.25 mmol) of Me_3Al (1 M solution in toluene) under argon at room temperature. The suspension was stirred for 2 h at 25 °C and cooled to −78 °C. To the resulting yellow solution were added 0.47 mL (3.75 mmol) of TMSCN and 0.13 mL (1.25 mmol) of PhCHO at −78 °C. After the solution was stirred for 5 h at −78 °C, the reaction was quenched by 2 N HCl, and the mixture was vigorously stirred for 10 min. The aqueous layer was extracted with ether, and the combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo to leave a yellow oil. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate = 7:1), after removal of the solvent, to afford 0.16 g (95%) of mandelonitrile.

Method B. To a suspension of 1.08 g (2.5 mmol) of Ts-S-Val-S-Phe-OMe in 40 mL of toluene was added 2.5 mL (2.5 mmol) of Me_3Al (1 M solution in toluene) under argon at rt, and the mixture was heated to 110 °C and stirred for 2 h. After the resulting suspension was cooled to −20 °C, and 0.94 mL (7.5 mmol) of TMSCN and 0.28 mL (2.5 mmol) of 2,2-dimethylpropionaldehyde were added. The mixture was stirred for 23 h at −20 °C, and the reaction was quenched with 2 N HCl, and the mixture was vigorously stirred for 10 min. The aqueous layer was extracted with ether, and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to leave a colorless oil. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate = 7:1), after removal of the solvent, to afford 0.21 g (76%) of the cyanohydrin of 2,2-dimethylpropionaldehyde.

Determination of the Enantiomeric Excess of Cyanohydrins: Method A (for Aromatic Aldehydes). To a small portion of the obtained crude cyanohydrin which contained unreacted aldehyde were added 0.50 mL (0.50 mmol) of (1R,2S,5R)-(−)-menthyl chloroformate (1 M solution in benzene) and 0.08 mL (1.0 mmol) of pyridine. After stirring for 12 h at rt, the suspension was passed through a silica gel short-path column. The eluate was concentrated to give a crude mixture of the corresponding diastereomeric (−)-menthyl carbonic esters. The diastereomeric excess was determined by ^{1}H NMR analysis.[5a,11]

Method B (for Aliphatic Aldehydes). To a small portion of the purified cyanohydrin were added 0.5 mL of CCl_4 and 6 drops of pyridine, followed by 2 drops of (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(+)-MTPA-Cl]. The suspension was stirred for 12 h at rt and passed through a silica gel short-path column. The eluate was concentrated to give a crude mixture of the corresponding diastereomeric MTPA esters. The diastereomeric excess was determined by gas chromatography.[5a,12]

Measurement of the ^{1}H NMR Spectrum of a Mixture of Peptide and Me_3Al. To 32.6 mg (0.1 mmol) of Nap-S-Val-NH^{t}Bu was added under argon 1.0 mL (0.1 mmol) of Me_3Al (0.1 M solution in benzene-d_6), and the suspension was stirred for 9 h at 25 °C. The resulting yellow solution was transferred to a NMR tube by a syringe under argon.

^{1}H NMR Spectrum of Nap-*S*-Val-NH^{t}Bu (2d) (C_6D_6): δ 14.96 (s, 1 H, OH), 8.70 (s, 1 H, CH=N), 7.65 (d, J = 8.5 Hz, 1 H, ArH), 7.42–7.45 (m, 1 H, ArH), 7.38 (d, J = 9.4 Hz, 1 H, ArH), 7.22–7.26 (m, 1 H, ArH), 7.09–7.20 (shielded with the solvent, 2 H, ArH), 5.81 (s, 1 H, NH), 3.53 (d, J = 4.3 Hz, 1 H, CαH), 2.47–2.59 (m, 1 H, CαCH), 1.25 (s, 9 H, *tert*-butyl CH_3), 1.01 (d, J = 6.8 Hz, 3 H, isopropyl CH_3), 0.75 (d, J = 6.8 Hz, 3 H, isopropyl CH_3).

^{1}H NMR Spectrum of the Mixture of Nap-*S*-Val-NH^{t}Bu (2d) and Me_3Al (5) (C_6D_6). δ 8.70 (s, 1 H, CH=N), 7.83 (d, J = 8.1 Hz, 1 H, ArH), 7.35–7.41 (m, 2 H, ArH), 7.28–7.32 (m, 1 H, ArH), 7.16 (d, J = 9.0 Hz, 1 H, ArH), 7.07–7.12 (m, 1 H, ArH), 5.65 (s, 1 H, NH), 3.16 (d, J = 6.0 Hz, 1 H, CαH), 1.84–1.97 (m, 1 H, CαCH), 1.19 (s, 9 H, *tert*-butyl CH_3), 0.76 (d, J = 6.8 Hz, 3 H, isopropyl CH_3), 0.71 (d, J = 6.8 Hz, 3 H, isopropyl CH_3), 0.09 (s, 3 H, $AlCH_3$), –0.25 (s, 3 H, $AlCH_3$).

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Supplementary Material Available: ^{1}H NMR spectra for compounds **2d**, **3b**, and the mixture of **2a** or **2d** and Me_3Al (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of (±)-γ-Lycorane by the Intramolecular Cycloaddition of an Azide with an ω-Chloroalkene

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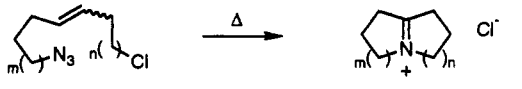
Cyclization of 1-[2-(chloromethyl)-4,5-(methylenedioxy)phenyl]-3-(2-azidoethyl)cyclohex-1-ene (**16**) in benzene at 140 °C caused the following sequence of events: (1) intramolecular 1,3-dipolar cycloaddition of the azide onto the alkene; (2) formation of an imine by loss of nitrogen from the triazoline intermediate with concomitant hydrogen migration; and (3) intramolecular N-alkylation of the imine nitrogen with the benzylic chloride. Without isolation, the resultant iminium ion was reduced with sodium borohydride to give (±)-γ-lycorane (**3**). The cyclization precursor **16** was prepared using a novel allylic substitution reaction, where the allylic alcohol **10** or the allylic acetate **11** was treated with 1-ethoxy-1-[(*tert*-butyldimethylsilyl)oxy]ethene and lithium perchlorate in ether to produce the γ,δ-unsaturated ester **12**. An alternative synthesis of (±)-γ-lycorane (**3**) was accomplished using a similar 1,3-dipolar cycloaddition approach, except that the benzylic chloride functionality was absent (i.e., **26** → **27**). Reduction of the resultant imine followed by a Bischler–Napieralski cyclization gave the known lactam **31**, which had previously been converted to (±)-γ-lycorane.

We have recently described a method for the generation of bicyclic iminium ions **2** in one operation from azides **1** (eq 1).[1,2] The reaction proceeds by an intramolecular 1,3-dipolar cycloaddition of an azide onto an alkene, producing an intermediate triazoline. Fragmentation of the triazoline and rearrangement to a monocyclic imine occurs, which is internally N-alkylated by the pendant alkyl chloride, delivering the iminium ion **2**. We now report the use of this methodology for the synthesis of (±)-γ-lycorane (**3**).



1 **2**

γ-Lycorane (**3**) is a representative of the lycorine class of Amaryllidaceae alkaloids.[3] While most of these alkaloids have a trans-B,C ring juncture (e.g., lycorine, **4**), compounds with a cis-B,C ring juncture such as that found in γ-lycorane have recently appeared, including fortucine (**5**)[4] and siculinine (**6**).[5] The biological activity of lycorine and related compounds includes antitumor activity, plant growth inhibition, and the inhibition of protein synthesis,[3] thus eliciting a considerable amount of interest in the synthesis of these alkaloids.[3,6,7] Most of the synthetic

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