and quenched mixture of the precursor peptide prepared as described in method 1 was added to the vial. The reaction was left in an ice bath with occasional shaking and was allowed to come to room temperature. After 3 h, 10 μL of DMF was added, the reaction mixture was centrifuged, and the supernatant was subjected to purification by HPLC as described above under method 1. The radiochemical yield was 25–27% in several trials. The peptide was identical with the previously prepared [D-Pen^2,4′-I-Phe^4,D-Pen^5]enkephalin.

Acknowledgment. This work was supported by a grant from U.S. Public Health Service Grant DK 17420 and DA 06284 and by the National Science Foundation.

Vanadium(II)-Promoted Cyclization of 5,6-Enals or 5,6-Ynals. A Stereoselective Approach to *trans*-2-Alkyl- or *trans*-2-Alkylidenecyclopentanols

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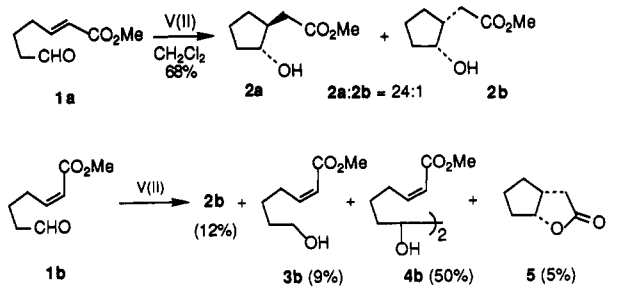
Received January 30, 1991

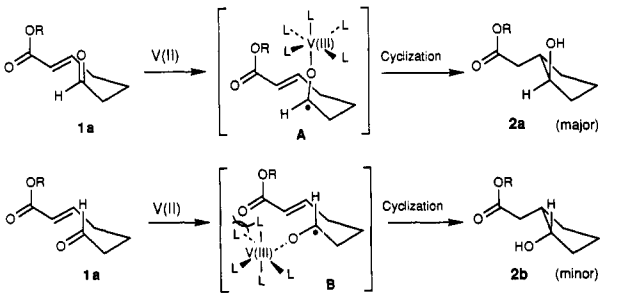
Reductive cyclization of δ,ε-enal or its keto version has found diverse applications in the synthesis of bioactive cyclopentanoids.[1] Low-valent metallic species such as zinc[2] and Sm(II)[3] as well as lithium naphthalenide[4] have been conveniently utilized for this purpose. Electroreduction in a divided cell system has also shown promise in the related conversion of an aldehyde–electron-deficient olefin[1a,5] or a ketone–normal olefin system.[6] Photoreduction is known to be effective for this purpose.[7] However, little attention has been paid to the diastereofacial selection of the process in spite of its potent applicability to the control of 1,2-relative stereochemistry. Recently, the bimetallic V(II) species, $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$, has been introduced by Pedersen et al. to achieve the stereoselective cross coupling of two different alkanals under the mild conditions,[8] referred to as an intermolecular pinacol cross-coupling reaction. This encouraging development coupled with the propensity of this V(II) reagent to generate metalated aldehyde ketyls prompted us to envisage a synthesis of cyclopentanols with α-substituents in a stereoselective manner employing various δ,ε-enals. We now report that the cyclization of 5,6-unsaturated aldehydes is promoted with this reagent to provide 2-alkyl- or 2-alkylidenecyclopentanols, in which the kind of olefin and its geometry are responsible for the stereochemical outcome.

The treatment of methyl (*E*)-7-oxo-2-heptenoate (**1a**)[5] with 2–3 equiv of $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$, freshly prepared from $VCl_3(THF)_3$ by the reduction with Zn,[8a] in dichloromethane at room temperature resulted in smooth cyclization to give **2a** in 68% yield. Relative stereochemistry at the C-1 and C-2 positions of newly constructed cyclopentanol was assigned to be **2a** with a ratio of 24:1 in favor of the trans isomer based on the ^{1}H NMR analysis.[9] The corresponding cis isomer was obtained as a mixture of the hydroxy ester **2b** and its lactone derivative. The similar conversion of **1a** into **2a** with the V(II) reagent

Scheme I



Scheme II



was conducted in the presence of *tert*-butyl alcohol as a proton donor to afford again the trans isomer **2a**, selectively (61%). However, in this case, the trans to cis ratio (**2a**:**2b**) decreased to 11:2, the cis isomer being obtained as the corresponding γ-lactone **5** (Scheme I).

It is noteworthy that the selectivity observed in this work is exceptionally high as compared with the previous reports in which a mixture of **2a** and **2b** was given in 69–70% yields with the ratios of 3.1:1 and 1.4:1 for the reduction of **1a** with Sm(II)[3] and the electroreduction of **1a** in a DMF–R_4NBF_4–(Pt)–(Hg) system,[5] respectively. Furthermore, trans selectivity increased when the methacrylate derivative **1c** was subjected to the present cyclization. Indeed, the formation of a cis isomer could not be detected at all by the ^{1}H NMR (500-MHz) analysis. A similar high level of trans selectivity was observed in the

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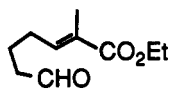
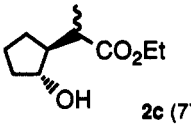
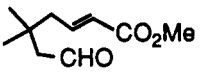
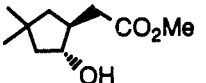
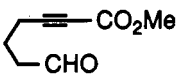
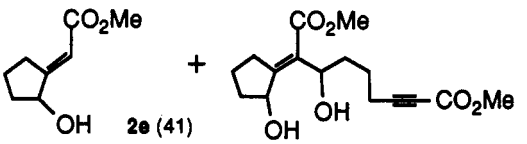
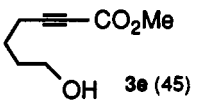
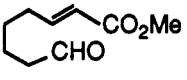
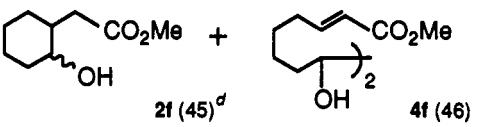
(9) We are thankful to Professor R. D. Little for providing us with the copies of IR and ^{1}H NMR spectra of *trans*- and *cis*-**2a** and -**2f**, which were prepared from the same starting material as that employed in our study by the electroreduction in a DMF–(Pt)–(Hg) system.[5]

0022-3263/91/1956-4983$02.50/0

Table I. Reductive Cyclization of Alkenals and Alkynals with $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$[a]

entry	substrate	time (h)	products (yield, %)
1	 1c	2	 2c (77)[c]
2	 1d	2	 2d (67)
3[b]	 1e	1	 2e (41) + 4e (59)
4	1e	20	2e (55) +  3e (45)
5	 1f	6	 2f (45)[d] + 4f (46)

[a] Carried out by using 0.2–0.5 mmol of the substrate and $VCl_3(THF)_3$ (3 equiv) + Zn (3 equiv) in CH_2Cl_2 at room temperature. [b] Carried out in CH_2Cl_2–THF. [c] Determined to be a 2.7:1 mixture at the α position of the ester moiety. [d] The *trans* to *cis* ratio was determined to be 5.4:1.

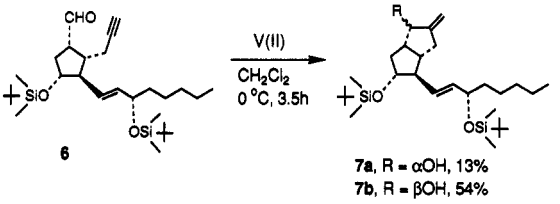
reductive cyclization of (*E*)-4,4-dimethyl-7-oxoheptenoate **1d**.

In order to gain more insight into the mechanistic aspects leading to the trans arrangement from the *E* olefin **1a**, we examined the reductive coupling of the *Z* isomer **1b**.[10] The reaction proceeded rather slowly compared with the *E* isomer **1a** and turned out to produce the pinacol **4b** as a major product (50% yield) along with a mixture of **2b** (12%), carbinol **3b** (9%), and γ-lactone **5** (5%). This result probably suggests that the trapping of the vanadium aldehyde ketyl intermediate (B in Scheme II) generated from **1b** with the *Z* enoate group was considerably retarded for steric reasons, which made the intermolecular process become the major course. In this context, the observed trans selectivity associated with the V(II)-promoted cyclization of **1a** should emerge through a spatial arrangement of the olefin moiety, which suited for an ensuing coupling process at the V(III)-aldehyde ketyl complex (A in Scheme II).[11]

The present method was found to be applicable to the cyclization of other acyclic aldehydes containing a double or a triple bond at the C-5,6 or C-6,7 position, the results of which are shown in Table I. The cyclization of the acetylenic aldehyde **1e** proceeded to give *anti*-2-alkylidene-1-cyclopentanol **2e** in 41–55% yields, but was accompanied with the formation of byproducts such as the dimeric product **4e** (59% yield) when run in CH_2Cl_2 and the carbinol **3e** (45% yield) in THF. The dimeric product **4e** is considered to form by the intermolecular radical coupling of the intermediary vinyl–vanadium complex with the formyl group of the second **1e**, while **3e** can be ascribed to hydrogen abstraction by the ketyl intermediate from THF. The cyclization of the aldehyde **1f** bearing the 6,7-enoate group was also feasible with this reagent to produce the corresponding 2-alkylcyclohexanol **2f** with a trans to cis ratio of 5.4:1 (entry 6). As the ene functionality located one additional methylene unit away from the formyl group as compared with the 5,6-alkenal **1a**, the reaction of **1f** became sluggish and was contaminated with a considerable intermolecular coupling to give the pinacol **4f** in 46% yield.[12]

To our delight, the cyclization of the 5,6-alkynal subunit assembled onto the cyclopentane ring **6**[13] in a cis fashion was easily effected by the action of the V(II) reagent to

Scheme III



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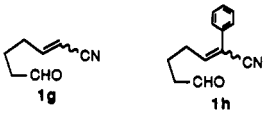
(12) Our attempt to cyclize the nitrile derivatives **1g** and **1h** were unsuccessful. In these cases, the addition of the nitriles **1g** and **1h** to the V(II) reagent in CH_2Cl_2 caused the immediate precipitation of unidentified solid materials presumably due to the complexation with the V(II) reagent.


1g 1h

(13) An optically pure **6** was supplied from Teijin Co. (Japan).

give the bicyclo[3.3.0] skeleton in 67% yield (Scheme III). This cyclization process may constitute an alternative entry to the key process developed by Noyori, Kurozumi, et al. in their synthesis of isocarbacyclin, an important chemotherapeutic agent, and realized by using lithium naphthalenide or Sm(II) reagent in 60–70% yields.[1b]

In conclusion, the V(III) aldehyde ketyls derived from alkanals bearing an internal activated *E* olefin or an acetylenic group lead to the cyclization products with a high trans selectivity. This intramolecular ketyl–alkene coupling process can compete with an intermolecular pinacol coupling depending on the kinds of an unsaturated bonds and their geometry.

Experimental Section

Starting aldehydes **1a**,[5] **1b**,[10] **1c**,[5] **1d**,[5] **1e**[10] and **1f**[6] were prepared in a similar manner as reported in the literature. Melting points and boiling points indicated by an air-bath temperature are uncorrected. IR spectra were recorded on a JASCO FT-5000 spectrometer. ^{1}H NMR spectra were taken in $CDCl_3$ (Me_4Si as an internal standard). Column chromatography was carried out with a Merck Kieselgel 60, Art. 7734 (silica gel) with hexane–AcOEt as an eluent.

Cyclization of Methyl (*E*)-7-Oxo-2-heptenoate (1a) with Vanadium(II) Reagent, a Typical Procedure. Freshly prepared pink powder of $VCl_3(THF)_3$ (560 mg, 1.5 mmol) was dried in a Schlenk tube under high vacuum for 10 min and then back-flushed with Ar. Dry CH_2Cl_2 (6 mL) and zinc dust (98 mg, 1.5 mmol) were added at room temperature under a pressure of Ar. The color of the solution changed from brown to green after being stirred for ca. 30 min, which secured the formation of divalent vanadium reagent. To the stirred suspension of this V(II) reagent in dry CH_2Cl_2 was added dropwise methyl (*E*)-7-oxo-2-heptenoate (**1a**, 76 mg, 0.5 mmol) at room temperature under Ar. After being stirred for 20 h, the mixture was poured into aqueous cold 5% tartaric acid (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with aqueous saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated under vacuum. The crude products were purified by column chromatography (SiO_2, hexane/AcOEt = 5/1) to give methyl *trans*-(2-hydroxycyclopentyl)acetate[5] (**2a**, 51.3 mg, 68%) as a colorless oil: bp 38–40 °C (0.2 Torr); IR (neat) 3360 (OH), 2958, 2876, 1740 (CO), 1439, 1346, 1265, 1197, 1178, 1139, 1096 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.16–1.26 (m, 1 H), 1.54–1.64 (m, 2 H), 1.67–1.77 (m, 1 H), 1.91–1.99 (m, 2 H), 2.03–2.13 (m, 1 H), 2.39 (dd, *J* = 16.3, 8 Hz, 1 H, CH_2CO), 2.45 (ddd, *J* = 16.3, 6.1, 1.0 Hz, 1 H, CH_2CO), 2.51 (br s, 1 H, OH), 3.68 (s, 3 H, OMe), 3.85 (m, 1 H, CHO); ^{13}C NMR (126 MHz) δ 21.83, 30.70, 34.26, 38.17, 44.35, 51.77, 78.85, 174.64.

Physical properties along with spectral data of selected compounds listed in Table I are as follows.

Ethyl *trans*-2-(2-hydroxycyclopentyl)propionate (2c; a mixture of diastereoisomers (73:27) at the C-2 position of the ester group): bp 40–43 °C (0.2 Torr); IR (neat) 3386 (OH), 2962, 2878, 1734 (CO), 1456, 1379, 1342, 1259, 1183, 1158, 1100, 1044, 986, 861, 733 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.15, 1.20 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.24, 1.25 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.22–1.32 (m, 1 H), 1.50–1.73 (m, 3 H), 1.79–2.01 (m, 3 H), 2.31, 2.50 (m, 1 H, $CHCO_2$), 2.37 (br s, 1 H, OH), 3.85–3.89, 4.00–4.04 (m, 1 H, CHO), 4.12, 4.14 (q, *J* = 7.1, 2 H, CH_2); ^{13}C NMR (126 MHz) δ 14.16 + 14.19, 14.46 + 16.18, 22.05 + 22.42, 28.53 + 29.28, 34.73 + 35.06, 41.74 + 43.58, 50.22 + 51.49, 60.42 + 60.56, 75.25 + 77.55, 176.91 + 177.36. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.39; H, 10.00.

Methyl *trans*-(2-hydroxy-4,4-dimethylcyclopentyl)-propionate (2d): bp 42–45 °C (0.2 Torr); IR (neat) 3376 (OH), 2956, 2868, 1725, 1439, 1367, 1267, 1209, 1154, 1079, 1013, 913, 735 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.00, 1.09 (s, 6 H, CH_3), 1.12 (m, 1 H, CH_2), 1.50 (m, 1 H, CH_2), 1.72 (m, 1 H, CH_2), 1.87 (m, 1 H, CH_2), 2.22–2.31 (m, 1 H, CH), 2.39–2.50 (m, 2 H, CH_2CO), 3.04 (br s, 1 H, OH), 3.69 (s, 3 H, OMe), 3.92 (m, 1 H, CHO); ^{13}C NMR (126 MHz) δ 30.61, 31.02, 36.04, 38.47, 43.88, 46.03, 49.21, 51.81, 78.66, 174.88. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.55; H, 9.65.

Methyl *anti*-(2-hydroxycyclopentylidene)acetate (2e): bp 43–45 °C (0.2 Torr); IR (neat) 3400 (OH), 2958, 2880, 1715 (CO), 1663, 1437, 1361, 1305, 1209, 1143, 1100, 1025, 965, 866 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.48–1.65 (m, 2 H), 1.65 (br s, 1 H, OH), 1.84–1.92 (m, 1 H), 2.02–2.08 (m, 1 H), 2.74–2:90 (m, 2 H), 3.69 (s, 3 H, OMe), 4.48 (m, 1 H, CHO), 5.96 (m, 1 H, CH=); ^{13}C NMR (126 MHz) δ 21.07, 30.22, 34.60, 51.07, 76.36, 112.73, 167.35, 168.14. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.30; H, 7.77.

Dimethyl 7,8-dihydroxy-2(*Z*),12(*Z*)-tetradecadienedioate (4b; a mixture of *dl* and meso isomers): IR (neat) 3370 (OH), 2950, 2866, 1723, 1647, 1439, 1408, 1180, 1116, 1075, 1019, 820, 731 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.42–1.58, 1.59–1.71 (m, 8 H), 1.98, 2.51 (br s, 1 H, OH), 2.55–2.64, 2.66–2.75 (m, 4 H, CH_2), 3.42, 3.67 (m, 1 H, CHO), 3.69 (s, 6 H, OMe), 5.78 (dt, *J* = 11.5, 1.6 Hz, 2 H, CH=), 6.22–6.27 (m, 2 H, CH=); ^{13}C NMR (126 MHz) δ 24.93, 25.27, 28.60, 30.56, 32.78, 51.07, 73.99, 74.09, 119.51, 150.43, 166.89.

Dimethyl 7-hydroxy-8-(2-hydroxycyclopentylidene)-2-nonanedioate (4e, less polar component): IR (neat) 3344 (OH), 2958, 2238, 1715 (CO), 1437, 1263, 1197, 1079, 754 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.62–1.70, 1.73–1.93 (m, 8 H), 2.33–2.45 (m, 2 H), 2.50–2.58 (m, 1 H), 2.81–2.88 (m, 1 H), 2.71 (br s, 2 H, OH), 3.74 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 4.75 (m, 1 H, CHO), 4.89 (m, 1 H, CHO); ^{13}C NMR (126 MHz) δ 18.23, 22.70, 24.09, 33.18 (2 C), 35.55, 51.50, 52.59, 70.69, 72.97, 73.03, 89.80, 129.63, 154.37, 159.46, 168.79. Polar component: IR (neat) 3290 (OH), 2958, 2238, 1700 (CO), 1437, 1261, 1197, 1079, 978, 754 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.57–1.65, 1.68–1.92 (m, 8 H), 2.38 (br s, 2 H, OH), 2.32–2.45 (m, 2 H), 2.51–2.58 (m, 1 H), 2.68–2.75 (m, 1 H), 3.75 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 4.68 (m, 1 H, CHO), 4.84 (m, 1 H, CHO); ^{13}C NMR (126 MHz) δ 18.42, 22.85, 24.11, 32.84, 34.79, 35.23, 51.51, 52.60, 70.69, 72.87, 73.19, 89.24, 129.42, 154.19, 159.05, 168.61.

Dimethyl 8,9-dihydroxy-2(*E*),14(*E*)-hexadecadienedioate (4f): IR (KBr) 3212, 2940, 1727, 1659, 1439, 1290, 1176, 980, 837, 663 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.30–1.57 (m, 12 H), 2.12–2.24 (m, 6 H, CH_2, OH), 3.37, 3.56 (m, 2 H, CHO), 3.70 (s, 3 H, OMe), 5.80 (dt, *J* = 15.6, 1.5 Hz, 2 H, CH=), 6.95 (dt, *J* = 15.6, 7.1 Hz, 2 H, CH=); ^{13}C NMR (126 MHz) δ 25.19, 25.53, 27.99, 30.95, 32.08, 33.34, 51.40, 74.22, 74.48, 120.98, 149.37, 167.15.

Acknowledgment. We thank "The SC-NMR Laboratory of Okayama University" for 500-MHz NMR measurements. The partial financial support by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan (63303009) is gratefully acknowledged. We deeply appreciate Teijin Co. for the generous supply of optically pure **6**. H.K. appreciates generous encouragement from Professor T. Sekiba of Toyama National College of Technology.

Supplementary Material Available: Spectral data of *cis*-**2f**, *trans*-**2f**, **7a**, and **7b** and ^{1}H NMR spectra of the compounds **4b**, **4e**, and **4f** (6 pages). Ordering information is given on any current masthead page.

A Simple Chromatographic Technique for the Purification of Organic Stannanes

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Received March 18, 1991

Organic stannanes have recently gained wide acceptance as useful synthons,[1] and in particular their use in palladium-catalyzed cross-coupling reactions has received widespread attention.[2] One particular problem associated

(1) Pereyre, M.; Quintard, J. P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987.

0022-3263/91/1956-4985$02.50/0