

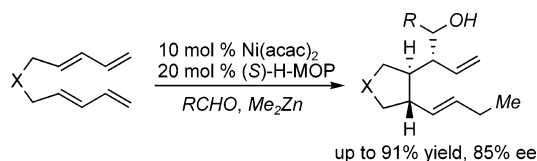
Nickel-Catalyzed Enantioselective Three-Component Coupling of Bis-1,3-dienes, Aldehydes, and Dimethylzinc

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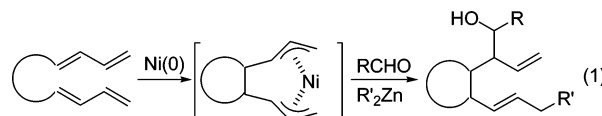
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Nickel-catalyzed three-component coupling of bis-1,3-dienes, aldehyde, and dimethylzinc was investigated. In the presence of catalytic amounts of Ni(acac)₂ and PPh₃, bis-1,3-dienes smoothly react with an aldehyde and dimethylzinc via intramolecular cyclodimerization of bis-1,3-diene moiety. The reaction proceeds through formation of a cyclic bis-allylnickel complex, insertion of an aldehyde, and addition of dimethylzinc to the resulting oxanickellacycle intermediate. An enantioselective coupling was also achieved by the use of a chiral monodentate phosphine ligand, H-MOP.

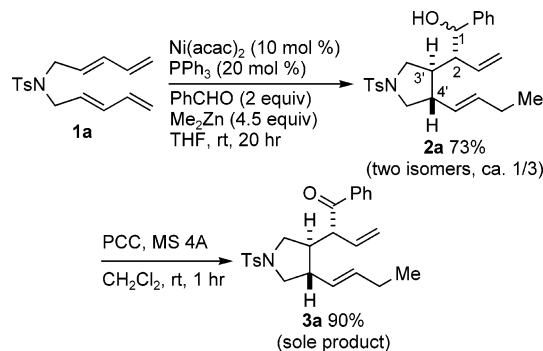
Dimerization of 1,3-dienes catalyzed by nickel complexes is an attractive process because of its ability to construct complex molecular skeletons.^{1,2} Another important category of nickel-catalyzed processes is reductive coupling of an unsaturated hydrocarbon and a carbonyl component with the assistance of a main-group organometallic reagent.^{3,4} As an integrated application of these two processes, we reported a nickel-catalyzed regio- and stereoselective carboxylative cyclization of bis-1,3-dienes that uses carbon dioxide as a carbonyl component.^{5a} An

enantioselective variant of this reaction was also very recently developed.^{5b} During the course of these studies, we thought that aldehydes should react with a bis-allylnickel complex in the presence of an organozinc reagent (eq 1). Herein, we present the results of our studies aimed at developing a three-component coupling reaction of bis-1,3-diene, aldehyde, and diorganozinc reagent.⁶



Reaction of bis-1,3-diene **1a** with benzaldehyde and dimethylzinc was first examined. In the presence of Ni(acac)₂ (10 mol %) and PPh₃ (20 mol %), **1a** was treated with benzaldehyde (2 equiv) and Me₂Zn (4.5 equiv) in THF. The reaction smoothly proceeded at room temperature to afford alcohol **2a** in 73% yield as an inseparable mixture of two isomers. Since it was thought that they were stereoisomers with respect to the stereochemistry of the hydroxyl group (C1), oxidation of this mixture with PCC was carried out and ketone **3a** was obtained in 90% yield as a sole product (Scheme 1). This result indicated

SCHEME 1



that the configuration of the other stereogenic centers (C2, C3', and C4') was controlled. This also showed that the reaction proceeded in a regioselective manner.

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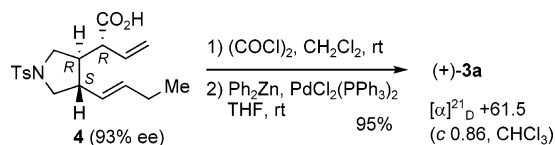
(2) For recent reports, see: (a) Hoberg, H.; Gross, S.; Milchereit, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 571. (b) Wender, P. A.; Nuss, M. J.; Smith, D. B.; Suarez-Sobrinho, A.; Vagberg, J.; Decosta, D.; Bordner, J. *J. Org. Chem.* **1997**, *62*, 4908. (c) Terao, J.; Oda, A.; Ikumi, A.; Nakamura, A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 3412.

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SCHEME 2



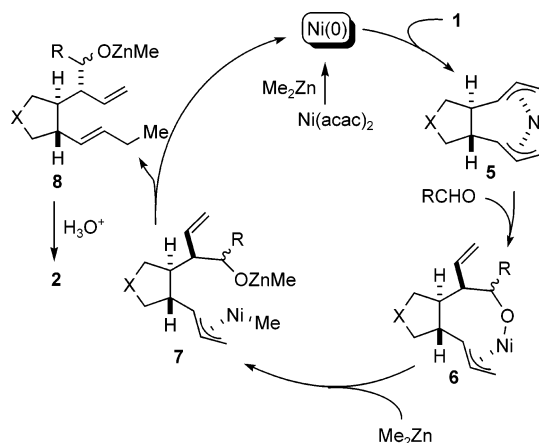
To elucidate the structure of ketone **3a** unequivocally, an independent synthesis of **3a** from carboxylic acid **4**, whose structure was determined in our previous work,⁵ was examined (Scheme 2). After treating **4** with oxalyl chloride, Negishi coupling of the resulting acyl chloride with Ph_2Zn was carried out to give a ketone (+)-**3a**,⁷ whose spectral data were identical with those of the compound obtained by oxidation of **2a**.

On the basis of similarities of regio- and stereoselectivities of this reaction to those of the carboxylative cyclization, a possible mechanism is considered as shown in Scheme 3. The reaction would start with oxidative cycloaddition of bis-1,3-diene **1** to Ni(0) complex⁸ to produce bis-allylnickel complex **5**, and subsequent insertion of an aldehyde into the nickel-carbon bond would afford oxanickellacycle **6**.⁹ Transmetalation of **6** with Me_2Zn would provide methylnickel complex **7**, which could easily undergo reductive elimination to afford zinc alkoxide **8**. Hydrolysis of **8** in an aqueous workup procedure should provide **2**.

The scope of this coupling reaction was next examined (Table 1). An aliphatic aldehyde, 1-butanal, was able to efficiently participate in a reaction with bis-1,3-diene **1a** (entry 1). The obtained product **2b** was readily converted into diastereomerically pure ketone **3b** after oxidation. Notably, paraformaldehyde also could be used as an aldehyde component. The reaction of **1a** with paraformaldehyde and Me_2Zn gave **2c** in 96% yield as a sole product (entry 2). Bis-1,3-diene **1b** also underwent the coupling reaction with these aldehydes in the same regio- and stereoselective manners to give the desired products **2d**, **2e**, and **2f** in high yields (entries 3–5).

To extend this coupling method to an enantioselective one, reactions using chiral phosphines were next exam-

SCHEME 3



ined. The use of MeO-MOP,¹⁰ which was the best ligand in the enantioselective carboxylative cyclization of bis-1,3-dienes,^{5b} resulted in a low yield of the coupling product (less than 10% yield of **2a** from **1a**). However, when the reaction of **1a** with benzaldehyde and Me_2Zn was carried out in the presence of 10 mol % of $\text{Ni}(\text{acac})_2$ and 20 mol % of (*S*)-H-MOP (see, Table 2),¹¹ **2a** was obtained in 58% yield as an inseparable mixture of two diastereomers (Table 2, entry 1). Oxidation of obtained **2a** gave ketone **3a** in 91% yield as a single isomer, whose enantiomeric excess (ee) was determined to be 81% by HPLC analysis with a chiral stationary phase column (DAICEL CHIRALPAK AD). The absolute configuration of **3b** obtained in this reaction was confirmed by comparison of its sign of specific optical rotation¹² with that of the aforementioned compound (+)-**3a**, which was prepared from chiral carboxylic acid **4** as shown in Scheme 2.

This method using H-MOP was further investigated. When **1a** was reacted with 1-butanal and Me_2Zn by using this method, **2b** was obtained in 51% yield (Table 2, entry 2). The ee of this reaction was determined to be 78% by conversion of **2b** into **3b**. This method was attractive in the case of the reaction with paraformaldehyde because **2c** was formed as a sole product with 85% ee in 93% yield (entry 3). Similar results were obtained from the enantioselective reaction of bis-1,3-diene **1b** with benzaldehyde and paraformaldehyde (entries 4 and 5).

In summary, a nickel-catalyzed regioselective three-component coupling of bis-1,3-diene, aldehyde, and dimethylzinc was developed. This reaction proceeds under mild conditions, and the coupling products can be obtained in optically active form when H-MOP is used as a ligand. Further investigation to expand the scope of this reaction is in progress.

Experimental Section

Typical Procedure for Nickel-Catalyzed Enantioselective Coupling Reaction with Benzaldehyde: (2*R*)-2-[(3*R*,4*S*)-4-[(*E*)-But-1-enyl]-1-(4-methylbenzenesulfonyl)pyrrolidin-3-yl]-1-phenylbut-3-en-1-ol (2a**).** To a solution of $\text{Ni}(\text{acac})_2$ (5.0 mg, 0.020 mmol) and (*S*)-H-MOP (17.2 mg, 0.039

(6) Tamaru and co-workers recently reported a similar multicomponent coupling reaction of 1,3-dien- ω -ynes with aldehydes and organozinc reagents. Kimura, M.; Ezoe, A.; Mori, M.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 201. See also ref 4a.

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(9) The observed regioselectivity in this insertion step is in contrast to that in Tamaru's report on nickel-catalyzed three-component coupling of 1,3-dien- ω -ynes (refs 5 and 4a), in which aldehydes selectively react at the less hindered terminus of the π -allylnickel intermediate. However, it is well-known that bis-allylnickel complexes or related palladium complexes preferentially react with an electrophile, such as CO_2 or H^+ , at a more hindered internal allylic carbon. The current result is accordant with these reports. For selected examples, see: (a) Sasaki, Y.; Inoue, Y.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.* **1976**, 605. (b) Jolly, P. W.; Stobbe, S.; Wilke, G.; Goddard, R.; Krüger, C.; Sektowski, J. C.; Tsay, Y.-H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 124. (c) Jolly, P. W. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 283. (d) Benn, R.; Jolly, P. W.; Mynott, R.; Raspel, B.; Schenker, G.; Schick, K. P.; Schoroth, G. *Organometallics*, **1985**, *4*, 1945. (e) Hoberg, H.; Gross, S.; Milchereit, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 571. (f) Jolly, P. W.; Mynott, R.; Raspel, B.; Schick, K. P. *Organometallics* **1986**, *5*, 473. (g) Takacs, J. M.; Clement, F.; Zhu, J.; Chandramouli, S. V.; Gong, X. *J. Am. Chem. Soc.* **1997**, *119*, 5804.

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TABLE 1. Nickel-Catalyzed Coupling Reaction of Bis-1,3-Diene, Aldehyde, and Dimethylzinc

entry	bis-diene	aldehyde (equiv)	Ni(acac) ₂ (mol %)	time (h)	products and yields	
					2	3
1	1a	<i>n</i> -C ₃ H ₇ CHO (2.0)	20	40	 2b (81%)	 3b (83%)
2	1a	(HCHO) _n (4.0)	10	5	 2c (96%, sole product)	
3	 1b	PhCHO (2.0)	20	16	 2d (82%)	 3d (73%)
4	1b	<i>n</i> -C ₃ H ₇ CHO (2.0)	20	45	 2e (84%)	 3e (80%)
5	1b	(HCHO) _n (4.0)	10	48	 2f (78%, sole product)	

TABLE 2. Enantioselective Coupling Reaction Using H-MOP^a

entry	bis-diene	aldehyde (equiv)	time (h)	yields (%)		ee (%)
				2	3	
1	1a	PhCHO (2.0)	18	58	91	81 ^b
2	1a	<i>n</i> -C ₃ H ₇ CHO (2.0)	25	51	80	78 ^b
3	1a	(HCHO) _n (4.9)	16	93		85 ^c
4	1b	PhCHO (2.0)	18	75	98	79 ^b
5	1b	(HCHO) _n (4.0)	18	86		85 ^c

^a Absolute configurations of all products were determined as illustrated above the body of the table. For details, see the Supporting Information. ^b Enantiomeric excesses of **3**. ^c Enantiomeric excess of **2**.

mmol) in THF (1.0 mL) was added a solution of bisdiene **1a**¹³ (59.6 mg, 0.20 mmol) in THF (2.7 mL) and benzaldehyde (0.040 mL, 0.39 mmol). The mixture was degassed by consecutive freeze/pump/thaw cycle (3 cycles). To the resulting solution was

added a solution of dimethylzinc (1.0 M in hexane, 0.74 mL, 0.74 mmol) at 0 °C. After the mixture had been stirred at room temperature for 18 h, the reaction mixture was hydrolyzed with a 10% aqueous solution of HCl at 0 °C, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc 3:1) to afford **2a** (colorless oil, 48.2 mg, 58%) as an inseparable mixture of two stereoisomers: IR (neat) 3529, 2960, 2932, 2873, 1734, 1637, 1598, 1464, 1343 cm⁻¹; ¹H NMR (data for major stereoisomer, 270 MHz, CDCl₃) δ 0.95 (t, *J* = 7.6 Hz, 3 H), 1.86–2.53 (m, 6 H), 2.43 (s, 3 H), 2.79–2.86 (m, 1 H), 3.03 (dd, *J* = 10.0, 8.5 Hz, 1 H), 3.24–3.36 (m, 2 H), 4.62 (d, *J* = 6.5 Hz, 1 H), 4.87–5.15 (m, 3 H), 5.46 (dt, *J* = 15.2, 6.4 Hz, 1 H), 5.68 (ddd, *J* = 17.0, 10.0, 10.0 Hz, 1 H), 7.13–7.36 (m, 7 H), 7.62–7.71 (m, 2 H); ¹³C NMR (data for major stereoisomer, 100 MHz, CDCl₃) δ 143.1, 142.0, 134.8, 134.6, 133.3, 129.3, 128.5, 128.1, 127.6, 127.3, 126.5, 120.0, 74.5, 53.4, 51.7, 44.4, 44.3, 25.6, 21.7, 13.7;

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(12) The ketone **3a** obtained by the procedures shown in Table 2 showed [α]_D²⁵ +60.9 (c 1.40, CHCl₃). For details, see the Experimental Section.

(13) (a) Takacs, J. M.; Lawson, E. *Organometallics* **1994**, *13*, 4787. (b) Takacs, J. M.; Clement, F.; Zhu, J.; Chandramouli, S. V.; Gong, X. *J. Am. Chem. Soc.* **1997**, *119*, 5804.

LR MS (EI, m/z) 425 (M^+), 319, 270. Anal. Calcd for $C_{25}H_{31}NO_3$: C, 70.55; H, 7.34; N, 3.19. Found: C, 70.42; H, 7.47; N, 3.19.

Oxidation of 2a to (2R)-2-[(3R,4S)-4-[(E)-But-1-enyl]-1-(4-methylbenzenesulfonyl)pyrrolidin-3-yl]-1-phenylbut-3-en-1-one (+)-3a. To a solution of **2a** (48.2 mg, 0.11 mmol) in CH_2Cl_2 (1.5 mL) was added a MS 4A (146 mg) and PCC (48.7 mg, 0.22 mmol) at 0 °C. After the mixture had been stirred at room temperature for 1.5 h, it was diluted with Et_2O at 0 °C and stirred for several minutes. The resulting suspension was filtered through a short column of Florisil (eluent, Et_2O). The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (hexane/ $EtOAc$ 4:1) to afford analytically pure product. The enantiomeric excess was determined to be 81% ee by HPLC analysis (DAICEL Chiralpak AD, hexane/2-propanol 9:1, 0.5 mL/min, UV detection at 220 nm, minor: 24.5 min, major: 30.0 min): $[\alpha]^{25}_D +60.9$ (c 1.40, $CHCl_3$, 81% ee); IR (neat) 2962, 2931, 2873, 1735, 1681, 1634, 1597, 1580, 1448, 1345 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, $J = 8.2$ Hz, 2 H), 7.66 (d, $J = 8.2$ Hz, 2 H), 7.56 (dd, $J = 7.9, 7.9$ Hz, 1 H), 7.44 (dd, $J = 7.9, 7.9$ Hz, 2 H), 7.29 (d, $J = 7.9$ Hz, 2 H), 5.70 (ddd, $J = 17.3, 11.2, 9.4$ Hz, 1 H), 5.32 (dt, $J = 15.3, 6.4$ Hz, 1 H), 5.16 (d, $J = 17.3$ Hz, 1 H), 5.15 (d, $J = 11.2$ Hz, 1 H), 5.04 (dd, $J = 15.3, 8.2$ Hz, 1 H), 4.01 (dd, $J = 9.4, 9.4$ Hz, 1 H), 3.49 (dd, $J = 9.9, 7.3$ Hz, 1 H), 3.32 (dd, $J = 10.2, 7.6$ Hz, 1 H), 3.03 (dd, $J = 10.2, 5.9$ Hz, 1 H), 2.85 (dd, $J = 9.9, 7.4$ Hz, 1 H), 2.59–2.68 (m, 1 H), 2.43–2.52 (m, 1 H), 2.43 (s, 3 H), 1.89 (qd, $J = 7.6, 6.4$ Hz, 2 H), 0.87 (t, $J = 7.6$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 143.2, 136.2, 134.7, 134.3, 133.1, 129.4, 128.4, 128.3, 128.2, 127.5, 119.6, 54.8, 53.1, 51.6, 45.7, 44.6, 25.6, 13.6; LR MS (EI, m/z) 423 (M^+), 268. Anal. Calcd for $C_{25}H_{29}NO_3$: C, 70.89; H, 6.90; N, 3.31. Found: C, 70.82; H, 6.96; N, 3.31.

Independent Preparation of (+)-3a from Optically Active Carboxylic Acid 4. To a solution of **4**¹⁴ (93% ee, 21.0 mg, 0.053 mmol) in CH_2Cl_2 (2 mL) was added oxalyl chloride (0.023 mL, 0.27 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h, then the solvent was evaporated in vacuo to afford crude acid chloride. This material was used in the following reaction without further purification.

To a suspension of $PdCl_2(PPh_3)_2$ (1.8 mg, 0.0027 mmol) in degassed THF (0.5 mL) was added Ph_2Zn (0.5 M in xylene, 0.16 mL, 0.074 mmol) and a solution of crude acid chloride in degassed THF (1.5 mL). After the mixture had been stirred at room temperature for 2 h, 10% aqueous HCl was added at 0 °C. The mixture was extracted with $EtOAc$. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, 6:1) to afford compound (+)-**3a** (21.6 mg, 95% from **4**,

colorless oil). The spectral data of this material were identical with those of the material obtained by oxidation of **2a**. The value of specific optical rotation also showed good accordance to that of (+)-**3a** obtained from **2a**: $[\alpha]^{25}_D +61.5$ (c 0.86, $CHCl_3$).

Typical Procedure for Nickel-Catalyzed Enantioselective Coupling Reaction with Paraformaldehyde: (2R)-2-[(3R,4S)-4-[(E)-But-1-enyl]-1-(4-methylbenzenesulfonyl)pyrrolidin-3-yl]but-3-en-1-ol (2c). To a mixture of Ni(acac)₂ (4.2 mg, 0.017 mmol), (*S*)-H-MOP (14.5 mg, 0.033 mmol), and paraformaldehyde (20.0 mg, 0.66 mmol) in THF (1.0 mL) was added a solution of bisdiene **1a** (50.0 mg, 0.17 mmol) in THF (1.7 mL). The mixture was degassed by consecutive freeze/pump/thaw cycle (3 cycles). To the resulting solution was added a solution of dimethylzinc (1.0 M in hexane, 0.74 mL, 0.74 mmol) at 0 °C. After the mixture had been stirred at room temperature for 16 h, the reaction mixture was hydrolyzed with 10% aqueous solution of HCl at 0 °C, and the aqueous layer was extracted with $EtOAc$. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 , and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ $EtOAc$ 3:2) to afford (–)-**2c** (54.0 mg, 93%) as a colorless oil. The enantiomeric excess was determined to be 85% ee by HPLC analysis (DAICEL Chiralpak AS, hexane/2-propanol 9:1, 0.5 mL/min, UV detection at 220 nm, major: 36.5 min, minor: 67.2 min): $[\alpha]^{25}_D -43.7$ (c 1.47, $CHCl_3$, 85% ee); IR (neat) 3531, 3072, 2962, 2931, 2875, 1639, 1597 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, $J = 8.2$ Hz, 2 H), 7.33 (d, $J = 8.2$ Hz, 2 H), 5.55 (ddd, $J = 17.0, 10.2, 9.4$ Hz, 1 H), 5.44 (dt, $J = 15.2, 8.0$ Hz, 1 H), 5.13 (d, $J = 10.2$ Hz, 1 H), 5.08 (dd, $J = 15.2, 8.0$ Hz, 1 H), 5.06 (d, $J = 17.0$ Hz, 1 H), 3.52 (dd, $J = 10.8, 5.3$ Hz, 1 H), 3.35–3.47 (m, 3 H), 3.03 (dd, $J = 9.7, 8.5$ Hz, 1 H), 2.87 (dd, $J = 9.7, 8.2$ Hz, 1 H), 2.43–2.54 (m, 1 H), 2.44 (s, 3 H), 2.11–2.19 (m, 1 H), 1.86–1.98 (m, 3 H), 1.60 (br, 1 H), 0.90 (t, $J = 7.6$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 136.7, 134.6, 133.1, 129.4, 128.1, 127.3, 118.6, 63.6, 53.3, 51.1, 48.7, 44.76, 44.69, 25.6, 21.7, 13.6; LR MS (EI, m/z) 349 (M^+), 319, 194, 155, 91. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 65.30; H, 7.79; N, 4.01. Found: C, 65.45; H, 7.62; N, 3.98.

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Supporting Information Available: Spectral data for all new compounds, general procedures for coupling reactions, and procedures for determination of the stereochemistry, enantiomeric excess, and absolute configuration. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) The optically active carboxylic acid **4** was prepared from **1a** according to the procedure reported in ref 5b. The absolute stereochemistry of **4** already has been determined in the same literature.