A New Asymmetric Synthesis of Cyanohydrins and Oxygen-Functionalized Derivatives: Stereoselective Addition of Cyanide to Chiral Rhenium Aldehyde and Ketone Complexes of the Formula $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(O{=}CRR')]^+BF_4^-$

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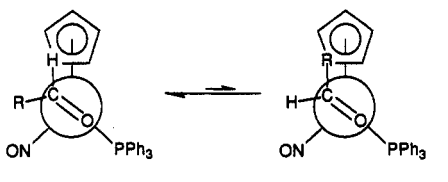
Reactions of racemic and optically active π aldehyde complexes $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(\eta^2\text{-}O{=}CHR)]^+ BF_4^-$ (1; R = **a**, CH_3; **b**, CH_2CH_3; **c**, $CH(CH_3)_2$; **d**, $CH_2C_6H_5$; **e**, C_6H_5) with $(CH_3CH_2)_4N^+ CN^-$ (CH_2Cl_2, −80 °C) give cyanohydrin alkoxide complexes $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(OCH(CN)R)$ (**3a–e**, 78–95%) in 89–53% de. Subsequent reactions of (+)-(*RS*)-**3a–e** with (−)-(*R*)-$C_6H_5(CH_3O)(F_3C)CC(=O)Cl$ (MTPA-Cl) and DMAP in C_6H_6 give optically active esters MTPA–OCH(CN)R (96–85%; 90–56% de). Analogous reactions of racemic σ-methyl ketone complexes $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(\eta^1\text{-}O{=}C(CH_3)R)]^+ BF_4^-$ (**2**; R = **a**, CH_3; **b**, CH_2CH_3; **c**, $CH(CH_3)_2$; **d**, $C(CH_3)_3$; **e**, C_6H_5) and $(CH_3CH_2)_4N^+ CN^-$ give alkoxide complexes $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(OCCH_3(CN)R)$ (**5a–e**, 60–88%) in 71–99% de. A similar reaction of **2e** and $(CH_3)_3SiC{\equiv}CLi$ gives $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(OCCH_3(C{\equiv}CSi(CH_3)_3)C_6H_5)$ (88%) in 94% de. Mechanisms of diastereoselection are briefly discussed.

Cyanohydrins and oxygen-functionalized derivatives are versatile intermediates in organic synthesis[1] and also have useful applications in materials science.[2] However, two problems complicate their accessibility from aldehyde and ketone precursors. First, the addition of HCN to some aromatic or cyclic ketones is thermodynamically unfavorable.[3] Second, a new stereocenter is usually generated, leading to mixtures of enantiomers or diastereomers. Thus, there has been considerable recent interest in asymmetric syntheses of cyanohydrins.[4–7]

We have previously shown that the chiral rhenium Lewis acid $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)]^+$ (I) binds one enantioface of aldehydes with extremely high selectivity, as illustrated in Scheme I.[8,9] These π complexes, $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(\eta^2\text{-}O{=}CHR)]^+BF_4^-$ (1), are easily prepared in high yields in racemic or optically active form[8] from the substitution-labile dichloromethane complex $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(ClCH_2Cl)]^+BF_4^-$.[10] Furthermore, they undergo stereoselective addition of deuteride to give α-deuterated primary alcohol derivatives of high enantiomeric

Scheme I. Ground-State Binding Properties of Reactants

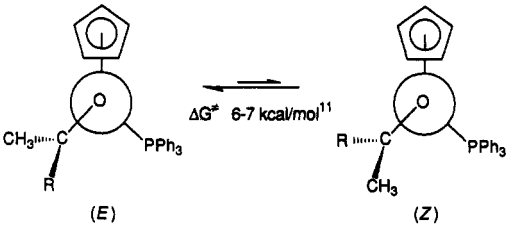
A. π-aldehyde complexes $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(\eta^2\text{-}O{=}CHR)]^+ BF_4^-$ (1)



(*RS*) (*RR*)

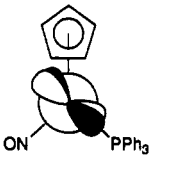
Equilibria:[9] R = alkyl 99:1
R = aryl (96-81):(4-19)

B. σ-ketone complexes $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(\eta^1\text{-}O{=}C(CH_3)R)]^+ BF_4^-$ (2)



(*E*) (*Z*)

C. HOMO of the pyramidal fragment $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)]^+$ (I)



I

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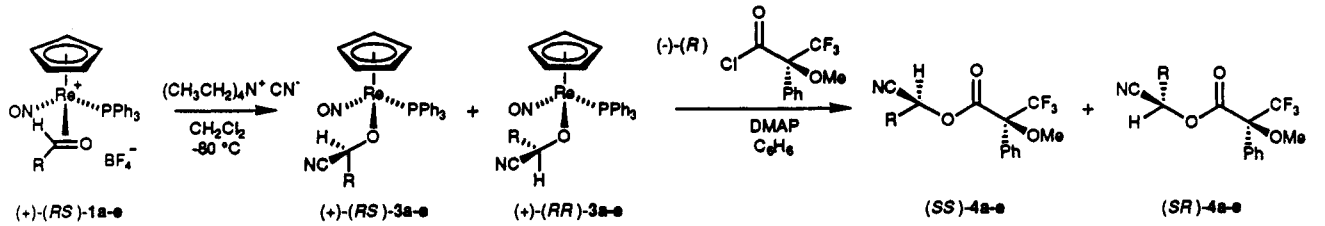
Scheme II. Addition of Cyanide to Racemic and Optically Active Aldehyde Complexes (±)-1 and (+)-(*R*)-1



R = a, CH_3
b, CH_2CH_3
c, $CH(CH_3)_2$
d, $CH_2C_6H_5$
e, C_6H_5

entry	starting material	ratio (±)-(*RS,SR*)-3 / (±)-(*RR,SS*)-3 or (+)-(*RS*)-3 / (+)-(*RR*)-3		yield (%)	ratio (*SS*)-4 / (*SR*)-4		yield (%)
1	(±) - **1a**	81.0:19.0	(62 % de)	87	———		—
2	(±) - **1b**	88.0:12.0	(76 % de)	88	———		—
3	(±) - **1c**	89.5:10.5	(79 % de)	90	———		—
4	(±) - **1d**	85.0:15.0	(70 % de)	85	———		—
5	(±) - **1e**	94.0: 6.0	(88 % de)	93	———		—
6	(+) - (*RS*) - **1a**	76.5:23.5	(53 % de)	84	78.0:22.0	(56 % de)	96
7	(+) - (*RS*) - **1b**	90.0:10.0	(80 % de)	92	90.0:10.0	(80 % de)	93
8	(+) - (*RS*) - **1c**	91.0: 9.0	(83 % de)	93	91.5: 8.5	(83 % de)	94 [a]
9	(+) - (*RS*) - **1d**	85.5:14.5	(71 % de)	78 [a]	84.0:16.0	(68 % de)	85
10	(+) - (*RS*) - **1e**	94.5: 5.5	(89 % de)	95	95.0: 5.0	(90 % de)	87

[a] Yield corrected for small amount of by-products as described in the experimental section.

and diastereomeric purities.[8] We have also shown that methyl ketones bind to I in a σ fashion, as illustrated in Scheme I.[11] The resulting complexes, $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(\eta^1\text{-}O{=}C(CH_3)R)]^+BF_4^-$ (**2**), undergo a similar hydride addition to give secondary alcohol derivatives of high enantiomeric and diastereomeric purities.[11]

We sought to extend the preceding addition chemistry to carbon nucleophiles. Accordingly, in this paper we report (1) the highly diastereoselective addition of *cyanide* ion to racemic and optically active aldehyde and ketone complexes **1** and **2** to give cyanohydrin alkoxide complexes of the formula $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(OCR(CN)R')$, (2) the facile incorporation of the alkoxide ligands into optically active "Mosher" esters, and (3) preliminary data with acetylide nucleophiles. Portions of this study have been communicated.[12]

Results

The racemic aldehyde complexes $[\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(\eta^2\text{-}O{=}CHR)]^+ BF_4^-$ (**1**; R = **a**, CH_3; **b**, CH_2CH_3; **c**, $CH(CH_3)_2$; **d**, $CH_2C_6H_5$; **e**, C_6H_5)[8] were suspended in CH_2Cl_2 at −80 °C. Then 1.05–1.10 equiv of solid $(CH_3CH_2)_4N^+ CN^-$ were added, and the mixtures were stirred at −80 °C. The sparingly soluble complexes **1a,e** required several hours to dissolve. After 16–18 h, chromatography on deactivated Florisil[13] gave the secondary cyanohydrin alkoxide complexes $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(OCH(CN)R)$ (**3a–e**) as red-orange foams in 85–93% yields. When CH_2Cl_2 *solutions* of $(CH_3CH_2)_4N^+ CN^-$ were similarly added to **1a–e** small amounts of the chloride complex $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(Cl)$[14] reproducibly formed.[15] This compound was chromatographically inseparable from products **3a–e**.

Subsequent ^1H NMR analysis showed **3a–e** to be 81–94:19–6 mixtures of *RS,SR/RR,SS* diastereomers (Scheme II, entries 1–5).[16,17] Diastereomer ratios were not affected by Florisil chromatography, as assayed by NMR spectra of crude and purified (+)-(*RS*)/(*RR*)-**3a,b,e** prepared below. The diastereomers were separable by preparative silica gel TLC, but recoveries were low.[13] Configurations at rhenium and carbon were assigned as described below and by analogy to previously reported deuteride additions.[8] In contrast to the primary alkoxide complexes $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(OCH_2R)$,[8] **3a–e** did not significantly decompose in solution or the solid state over periods of hours in air.

Complexes **3a–e** were characterized by microanalyses (Experimental Section) and IR and NMR (^1H, ^{13}C, ^{31}P) spectroscopy (Table I). As a result of the small quantities formed, only partial NMR assignments could be made for

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(13) Without Florisil deactivation (or on silica gel), variable amounts of **3a–e** were retained.

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(15) NMR experiments under homogeneous conditions show that cyanide addition is complete within a few minutes at −80 °C.

(16) The absolute configurations of the rhenium stereocenters in **3**, **5**, and **6** are specified first and assigned as described previously.[8] For the carbon stereocenter in **6**, the priority sequence $(CH_3)_3SiC{\equiv}C- > C_6H_5 (> HC{\equiv}C-)$ is employed (*J. Org. Chem.* **1970**, *35*, 2849). Since samples of (+)-(*RS*)-**3a–e** were not isolated in diastereomerically pure form, optical rotations were not measured. However, they are assumed to be dextrorotatory by analogy to other rhenium complexes with the same relative configuration.[8,10,11,14] The absolute configurations of the —O-CH(CN)R carbons in the Mosher esters **4** are specified first.

(17) Diastereomer ratios of rhenium complexes were determined by integrations of the cyclopentadienyl ^1H NMR resonances. The numerical components of diastereomer ratios are judged to be accurate to ±2, i.e., 93:7 ≡ (93 ± 2):(7 ± 2). The data in Schemes II and III are expressed to the nearest half-interger in order to facilitate conversion to % de.

Table I. Spectroscopic Characterization of Alkoxide Complexes (η^5-C_5H_5)Re(NO)(PPh_3)(OCR(C≡X)R')

complex (R/R')	IR ν_{NO} (cm^{-1}, KBr)	^1H NMR[a] (δ)	$^{13}C\{^1H\}$ NMR[b] (ppm)	$^{31}P\{^1H\}$ NMR[c] (ppm)
(*RS,SR*)-**3a** (H/CH_3)	1627 vs	7.62–6.96 (m, $3C_6H_5$), 5.01 (s, C_5H_5), 4.43 (q, J = 6.7, HCO), 1.03 (d, J = 6.6, CH_3)	PPh_3 at 134.9 (d, J = 51.4, *i*), 134.2 (d, J = 10.4, *o*), 130.4 (s, *p*), 128.5 (d, J = 10.4, *m*); 125.0 (s, CN), 90.7 (s, C_5H_5), 80.4 (d, J = 6.6, OC), 25.0 (s, CH_3)	18.5 (s)
(*RR,SS*)-**3a**[d] (CH_3/H)		4.83 (s, C_5H_5), 4.33 (q, J = 6.7, HCO), 1.16 (d, J = 6.6, CH_3)	90.6 (s, C_5H_5), 77.7 (d, J = 7.5, OC), 25.7 (s, CH_3)	17.9 (s)
(*RS,SR*)-**3b** (H/CH_2CH_3)	1636 vs	7.63–6.97 (m, $3C_6H_5$), 5.05 (s, C_5H_5), 4.46 (dd, J = 5.3, 6.4, HCO), 1.30–1.45 (m, CH_2), 0.80 (t, J = 7.4, CH_3)	PPh_3 at 134.9 (d, J = 51.3, *i*), 134.3 (d, J = 10.7, *o*), 130.4 (d, J = 2.1, *p*), 128.5 (d, J = 10.3, *m*); 124.3 (s, CN), 90.7 (d, J = 2.1, C_5H_5), 86.7 (d, J = 6.9, OC), 31.8 (s, CH_2), 9.2 (s, CH_3)	18.3 (s)
(*RR,SS*)-**3b**[d] (CH_2CH_3/H)		4.75 (s, C_5H_5), 4.05 (t, J = 6.6, HCO)	123.9 (s, CN), 32.5 (s, CH_2), 9.6 (s, CH_3)	18.2 (s)
(*RS,SR*)-**3c** (H/$CH(CH_3)_2$)	1636 vs	7.65–6.97 (m, $3C_6H_5$), 5.06 (s, C_5H_5), 4.44 (d, J = 4.5, HCO), 1.55–1.68 (m, $HC(CH_3)_2$), 0.84 (d, J = 6.6, CH_3), 0.83 (d, J = 6.6, $'CH_3$)	PPh_3 at 135.0 (d, J = 51.3, *i*), 134.2 (d, J = 10.5, *o*), 130.5 (d, J = 2.4, *p*), 128.1 (d, J = 10.2, *m*); 123.4 (s, CN), 92.0 (d, J = 6.9, OC), 90.8 (d, J = 1.9, C_5H_5), 35.9 (s, $C(CH_3)_2$), 18.2 (s, CH_3), 17.4 (s, $'CH_3$)	18.2 (s)
(*RR,SS*)-**3c**[d] ($CH(CH_3)_2$/H)		4.68 (s, C_5H_5), 0.80 (d, J = 6.6, CH_3), 0.79 (d, J = 6.6, $'CH_3$)	123.1 (s, CN), 90.4 (d, J = 1.9, C_5H_5), 36.6 (s, $C(CH_3)_2$), 18.3 (s, CH_3), 18.0 (s, $'CH_3$)	18.7 (s)
(*RS,SR*)-**3d** (H/$CH_2C_6H_5$)	1641 vs	7.57–6.98 (m, $4C_6H_5$), 5.00 (s, C_5H_5), 4.75 (dd, J = 6.7, 5,6, CHO), 2.60–2.65 (m, CH_2)	PPh_3 at 134.9 (d, J = 51.5, *i*), 134.3 (d, J = 10.6, *o*), 130.5 (d, J = 2.2, *p*), 128.6 (d, J = 10.2, *m*); CPh at 137.1 (s), 135.2 (s), 130.3 (s), 126.6 (s); 124.0 (s, CN), 90.7 (d, J = 2.1, C_5H_5), 86.0 (d, J = 6.6, OC), 45.2 (s, CH_2)	19.0 (s)
(*RR,SS*)-**3d**[d] ($CH_2C_6H_5$/H)		4.44 (s, C_5H_5)	123.6 (s, CN), 90.5 (d, J = 2.0, C_5H_5)	18.4 (s)
(*RS,SR*)-**3e** (H/C_6H_5)	1640 vs	7.57–6.93 (m, $4C_6H_5$), 5.60 (s, HCO), 5.07 (s, C_5H_5)	PPh_3 at 134.8 (d, J = 51.6, *i*), 134.1 (d, J = 10.7, *o*), 130.4 (d, J = 2.2, *p*), 128.6 (d, J = 10.3, *m*); CPh at 142.0 (s), 128.4 (s), 126.6 (s);[e] 123.8 (s, CN), 90.7 (d, J = 1.9, C_5H_5), 87.6 (d, J = 6.7, OCH)	17.8 (s)
(*RR,SS*)-**3e**[d] (C_6H_5/H)		4.65 (s, C_5H_5)	90.3 (d, J = 1.9, C_5H_5), 86.8 (d, J = 6.7, OCH)	18.8 (s)
5a (CH_3/CH_3)	1631 vs	7.58–6.98 (m, $3C_6H_5$), 5.15 (s, C_5H_5), 1.44 (s, CH_3), 1.19 (s, $'CH_3$)	PPh_3 at 135.1 (d, J = 51.4, *i*), 134.4 (d, J = 10.0, *o*), 130.4 (s, *p*);[e] 126.6 (s, CN), 90.5 (s, C_5H_5), 78.5 (d, J = 15.7, OC), 32.5 (s, CH_3), 32.3 (s, $'CH_3$)	18.0 (s)
(*RS,SR*)-**5b** (CH_3/CH_2CH_3)	1633 vs	7.57–6.98 (m, $3C_6H_5$), 5.16 (s, C_5H_5), 1.47 (s, $OCCH_3$), 1.43 (q, J = 7.1, CH_2), 0.94 (t, J = 7.3, CH_2CH_3)	PPh_3 at 135.0 (d, J = 51.1, *i*), 134.4 (d, J = 10.4, *o*), 130.4 (d, J = 2.4, *p*), 128.6 (d);[f] 126.5 (s, CN), 90.9 (d, J = 2.0, C_5H_5), 83.2 (d, J = 6.6, OC), 38.1 (s, CH_2), 31.2 (s, $OCCH_3$), 10.1 (s, CH_2CH_3)	18.3 (s)
(*RR,SS*)-**5b**[d] (CH_2CH_3/CH_3)		7.57–6.98 (m, $3C_6H_5$), 5.13 (s, C_5H_5), 1.15 (s, $OCCH_3$), 1.00 (t, J = 7.3, CH_2CH_3)	PPh_3 at 134.4 (d, J = 10.3); 90.7 (d, J = 2.1, C_5H_5)	17.9 (s)
(*RS,SR*)-**5c** (CH_3/$CH(CH_3)_2$)	1634 vs	7.57–6.98 (m, $3C_6H_5$), 5.16 (s, C_5H_5), 1.47 (s, $OCCH_3$), 1.44 (sep, J = 6.8, CH), 0.94 (d, J = 6.8, $CHCH_3$), 0.82 (d, J = 6.7, $CH'CH_3$)	PPh_3 at 135.1 (d, J = 50.7, *i*), 134.4 (d, J = 10.4, *o*), 130.0 (d, J = 2.4, *p*), 128.5 (d, J = 10.9, *m*); 126.1 (d, J = 1.1, CN), 91.1 (d, J = 2.1, C_5H_5), 87.4 (d, J = 6.6, OC), 40.9 (s, $OCCH_3$), 28.7 (s, CH), 19.3 (s, $CHCH_3$), 17.8 (s, $CH'CH_3$)	18.4 (s)
(*RR,SS*)-**5c**[d] ($CH(CH_3)_2$/CH_3)		7.57–6.98 (m, $3C_6H_5$), 5.03 (s, C_5H_5), 1.55 (s, $OCCH_3$), 1.06 (d, J = 6.9, $CHCH_3$), 0.77 (d, J = 6.7, $CH'CH_3$)		17.3 (s)
(*RS,SR*)-**5d** (CH_3/$C(CH_3)_3$)	1640 vs	7.56–6.98 (m, $3C_6H_5$), 5.16 (s, C_5H_5), 1.55 (s, $OCCH_3$), 0.87 (s, $C(CH_3)_3$)	PPh_3 at 135.4 (d, J = 50.8, *i*), 134.3 (d, J = 10.5, *o*), 130.4 (d, J = 2.3, *p*), 128.5 (d, J = 10.2, *m*); 126.5 (s, CN), 91.4 (s, C_5H_5), 91.0 (d, J = 6.0, OC), 39.9 (s, $C(CH_3)_3$), 25.8 (s, $C(CH_3)_3$), 25.0 (s, $OCCH_3$)	18.7 (s)
(*RS,SR*)-**5e** (CH_3/C_6H_5)	1655 vs	7.60–6.95 (m, $3C_6H_5$), 5.12 (s, C_5H_5), 1.88 (s, CH_3)	PPh_3 at 135.1 (d, J = 50.8, *i*), 134.4 (d, J = 10.6, *o*), 130.5 (s, *p*), 128.7 (d, J = 10.3, *m*); CPh at 127.5 (s), 127.1 (s), 125.8 (s);[e] 126.4 (s, CN), 91.4 (s, C_5H_5), 86.2 (d, J = 6.5, OC), 35.4 (s, CH_3)	18.7 (s)
(*RR,SS*)-**5e**[d] (C_6H_5/CH_3)		7.60–6.95 (m, $3C_6H_5$), 4.96 (s, C_5H_5), 1.59 (s, CH_3)	PPh_3 at 130.4 (s, *p*); 90.3 (s, C_5H_5)	18.4 (s)
(*RS,SR*)-**6** (CH_3/C_6H_5)	1636 vs	7.60–6.94 (m, $4C_6H_5$), 5.06 (s, C_5H_5), 1.95 (s, $OCCH_3$), 0.30 (s, $Si(CH_3)_3$)	PPh_3 at 135.1 (d, J = 49.6, *i*), 134.5 (d, J = 9.5, *o*), 130.7 (d, J = 2.1, *p*), 128.5 (d, J = 10.0, *m*); CPh at 150.9 (s), 126.6 (s), 126.2 (s);[e] 117.1 (s, SiCC), 90.6 (d, J = 1.4, C_5H_5), 89.0 (s, SiCC), 83.6 (d, J = 8.5, OC), 37.8 (s, $OCCH_3$), 0.6 (s, $Si(CH_3)_3$)	18.6 (s)
(*RR,SS*)-**6**[d] (C_6H_5/CH_3)		4.97 (s, C_5H_5), 1.90 (s, $OCCH_3$), 0.18 (s, $Si(CH_3)_3$)		

[a] At 300 MHz and ambient probe temperature in C_6D_6 and referenced to internal $(CH_3)_4Si$; all couplings (Hz) are to hydrogen. [b] At 75 MHz and ambient probe temperature in C_6D_6 and referenced to internal $(CH_3)_4Si$; all couplings (Hz) are to phosphorus. Assignments of PPh_3 carbon resonances were made as described in footnote c of Table I in: Buhro, W. E.; Georgiou, S.; Fernández, J. M.; Patton, A. T.; Strouse, C. E.; Gladysz, J. A. *Organometallics* **1986**, *5*, 956. [c] At 32.2 MHz and ambient probe temperature in C_6D_6 and referenced to external 85% H_3PO_4. [d] Only partial NMR data could be obtained for the minor diastereomers formed in Schemes II and III and eq 1. [e] One phenyl carbon obscured by solvent. [f] One line of doublet obscured by solvent.

the minor *RR,SS* diastereomers. Spectroscopic properties generally resemble those of the analogous primary alkoxide complexes.[8] However, the IR ν_{NO} are slightly greater (1627–1641 vs 1607–1622 cm^{-1}), suggesting lower π basicity

at rhenium. The cyclopentadienyl ^{1}H NMR resonances of (*RS,SR*)-**3a–e** (δ 5.00–5.07) are downfield of those of (*RR,SS*)-**3a–e** (δ 4.44–4.83), while those of the corresponding primary alkoxide complexes are usually intermediate (δ 4.76–4.96). The cyanide carbons in **3a–e** exhibit ^{13}C NMR resonances at 123–125 ppm. However, IR ν_{CN} were not observed and are presumed to be very weak.

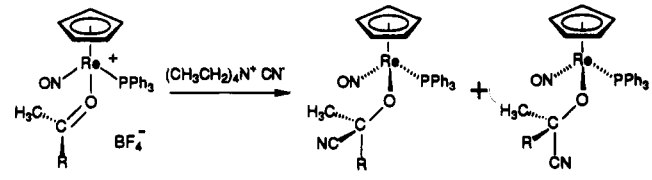
The optically active aldehyde complexes (+)-(*RS*)-**1a–e**[8] have been noted to be much more soluble than the racemates. Thus, CH_2Cl_2 *solutions* of (+)-(*RS*)-**1a–e** were similarly treated with solid $(CH_3CH_2)_4N^+$ CN^- at –80 °C. Identical workups gave optically active cyanohydrin complexes (+)-**3a–e** in 78–95% yields and as 76.5–94.5:23.5–5.5 mixtures of *RS*/*RR* diastereomers (Scheme II, entries 6–10).[16,17] The difference in diastereoselectivity between cyanide addition to racemic and optically active **1a** (entries 1 and 6) was reproducible. Possible explanations include the heterogeneity of the former reaction, and/or "nonlinear" stereoselectivity effects.[8,18]

Attention was next turned to detaching the cyanohydrin alkoxide ligands from the rhenium. The rhenium-oxygen linkages in analogous primary and secondary alkoxide complexes have been shown to be extremely reactive toward electrophiles such as protic acids, silylating agents, and acylating agents.[8,11] Thus, (+)-**3a–e**, the base DMAP (1 equiv), and the acid chloride (–)-(*R*)-C_6H_5-$(CH_3O)(F_3C)CC(=O)Cl$ ((–)-(*R*)-MTPA-Cl,[19] 2 equiv) were combined in C_6H_6 at room temperature (Scheme II). After 16–18 h, workup gave the optically active Mosher esters MTPA-OCH(CN)R (**4a–e**) in 96–85% yields. Analysis by capillary GLC (average of 4–6 injections) and ^{1}H NMR showed **4a–e** to be 78–95:22–5 mixtures of *SS*/*SR* diastereomers.[16] In all cases, the diastereomer ratios closely matched those of the precursor alkoxide complexes. The rhenium fragment was converted to the chloride complex (η^5-C_5H_5)Re(NO)(PPh_3)(Cl), which is of moderate configurational stability under the reaction conditions.[14]

The Mosher esters **4d–e** have been reported previously,[5c,6a] but without any spectroscopic characterization. Thus, diagnostic NMR data for **4a–e** are provided in the Experimental Section, and full data are given in the supplementary material. The absolute configurations of the cyanohydrin carbons in **4a–e** were assigned from established ^{1}H NMR shielding trends.[20] These in turn allowed configurational assignments in cyanohydrin alkoxide complexes (+)-**3a–e** that matched, in a relative sense, those previously established for products of deuteride addition to (+)-(*RS*)-**1a–e**.[8]

An independent confirmation of stereochemistry was sought. Thus, (+)-(*RS*)-**3e** was treated with the sulfonic acid *p*-$CH_3C_6H_4SO_3H$ (1.2 equiv, CH_2Cl_2, 0 °C). The reaction was complete within 5 min, as assayed by silica gel TLC. Column chromatography gave benzaldehyde cyanohydrin (71%, ≥95% purity) that was levorotatory ([α] –42° ± 1°, *c* 30 mg/mL, $CHCl_3$; lit.[6a] (*R*) [α] 49°), indicative of the *S* absolute configuration at carbon.[21] Also, the tosylate complex (+)-(*R*)-(η^5-C_5H_5)Re(NO)(PPh_3)(OSO_2-*p*-$C_6H_4CH_3$) was isolated in 52% yield ([α] 432° ± 10°, *c* 0.2 mg/mL, CH_2Cl_2; lit.[14] [α] 453°). These data establish retention of configuration at rhenium and an optical purity of 95 ± 2%. No attempts were made to optimize the chemical or optical yields of the products.

Scheme III. Addition of Cyanide to Racemic Ketone Complexes (±)-2. Only One Enantiomer of Each Product Diastereomer Is Depicted



(±)-**2a–e**
R = a, CH_3
b, CH_2CH_3
c, $CH(CH_3)_2$
d, $C(CH_3)_3$
e, C_6H_5

(*RS,SR*)-**5a–e** (*RR,SS*)-**5a–e**

	reaction temp = –80 °C ratio			reaction temp = 22 °C ratio	
starting material	(*RS,SR*)-**5** / (*RR,SS*)-**5**		yield (%)	(*RS,SR*)-**5** / (*RR,SS*)-**5**	
(±)-**2a**	——	——	60	——	——
(±)-**2b**	85.5:14.5	(71% de)	70	81.0:19.0	(62% de)
(±)-**2c**	97.5: 2.5	(95% de)	79	97.0: 3.0	(94% de)
(±)-**2d**	99.5:≤0.5	(≥99% de)	75	99.5:≤0.5	(≥99% de)
(±)-**2e**	92.5: 7.5	(85% de)	88	87.0:13.0	(74% de)

Next, the racemic σ methyl ketone complexes [(η^5-C_5H_5)Re(NO)(PPh_3)(η^1-O=C(CH_3)R)]$^+$ BF_4^- (**2**; R = **a**, CH_3; **b**, CH_2CH_3; **c**, $CH(CH_3)_2$; **d**, $C(CH_3)_3$; **e**, C_6H_5) were dissolved in CH_2Cl_2 and similarly treated with $(CH_3CH_2)_4N^+$ CN^- at –80 °C. Subsequent CaO chromatography gave the tertiary cyanohydrin alkoxide complexes (η^5-C_5H_5)Re(NO)(PPh_3)(OCCH_3(CN)R) (**5a–e**) as red-orange foams in 88–60% yields (Scheme III). Analysis by ^{1}H NMR showed **5b–e** to be 99.5–85.5:0.5–14.5 mixtures of *RS,SR*/*RR,SS* diastereomers.[16,17]

Configurations at rhenium and carbon in **5b–e** were assigned by analogy to previously reported hydride additions.[11] Diastereomer ratios were not affected by CaO chromatography, as assayed by ^{1}H NMR analysis of crude **5b**. However, minor byproducts were not completely removed. Nonetheless, spectroscopic purities were in all cases ≥92%. Chromatography on more strongly absorbing supports appeared to degrade yields and diastereomer ratios.

Reactions of **2b–e** and $(CH_3CH_2)_4N^+$ CN^- were repeated at room temperature. In most cases, lower diastereoselectivities were obtained (Scheme III). This facilitated the assignment of NMR resonances to the minor *RR,SS* diastereomers. However, within detection limits (≤0.5%), methyl *tert*-butyl ketone complex **2e** gave only the *RS,SR* diastereomer of **5e**. The spectroscopic properties of **5a–e** are summarized in Table I. The cyclopentadienyl ^{1}H NMR resonances of the *RS,SR* diastereomers were downfield of those of the *RR,SS* diastereomers. Also, the cyclopentadienyl ^{1}H and ^{13}C NMR resonances of **5a–e** were slightly downfield of those of secondary analogues **3a–e**. However, spectroscopic properties were in general quite similar.

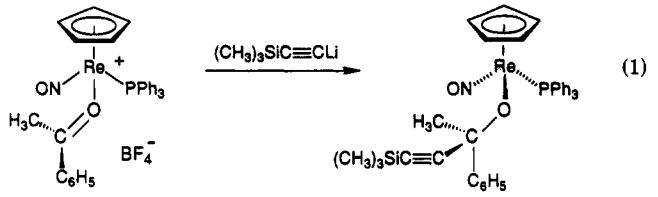
(18) (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (b) Terada, M.; Mikami, K.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1623. (c) Wynberg, H. *Chemia* **1989**, *11*, 150. (d) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353.

(19) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(20) The OCH(CN)R ^{1}H NMR resonances of (*SS*)-**4a–e** are upfield of those of (*SR*)-**4a–e**, as rationalized by a syn orientation of the phenyl ring in a conformational model developed by Mosher.[19b] This correlation has been verified by many independent syntheses. A second empirical trend is also found: the OCH_3 ^{1}H NMR resonances of (*SS*)-**4a–e** (syn to the cyanide in the Mosher model) are 0.1–0.2 ppm downfield of those of (*SR*)-**4a–e**. See also: Ohtani, I.; Kusumi, K.; Kashman, Y.; Kaksawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(21) Jacques, J.; Gros, C.; Bourcier, S. In *Stereochemistry, Fundamentals, and Methods*; Kagan, H. B., Ed.; Georg Thieme: Stuttgart, 1077; Vol. 4, p 237.

Finally, analogous additions of another class of triply bound carbon nucleophiles, acetylide ions, were briefly probed. Thus, acetophenone complex **2e** and $(CH_3)_3Si$-C≡CLi were reacted at −80 °C (eq 1). Workup gave the



2e (*RS,SR*)-**6** (94% de; racemic)

propargylic alkoxide complex $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(OCCH_3(C{\equiv}CSi(CH_3)_3)C_6H_5)$ (**6**) in 88% yield as a 97:3 mixture of *RS,SR*/*RR,SS* diastereomers.[16,17] This diastereomer ratio and that for **5e** are slightly lower than those reported earlier.[12b] Configurations were assigned by analogy to the cyanide additions, and spectroscopic properties are summarized in Table I. When this reaction was repeated at room temperature, **6** was isolated in 84% yield as a 82:18 mixture of diastereomers.

Discussion

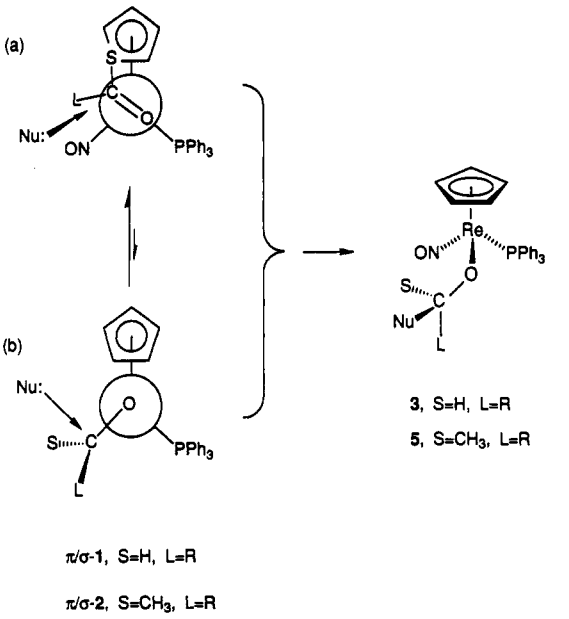
Schemes II and III show that a variety of cyanohydrin alkoxide complexes can be prepared in good to high yields and diastereomeric excesses from π aldehyde complexes **1a–e** and σ-methyl ketone complexes **2a–e**. It has been further demonstrated that the alkoxide ligands in the aldehyde-derived complexes (+)-(*RS*)-**3a–e** are readily incorporated into optically active organic esters. However, it should be emphasized that further refinements in these procedures are readily envisioned.

First, practical chromatographic separations of the diastereomers of **3a–e** and **5b–d** can undoubtedly be developed. This would allow the isolation of diastereomerically and enantiomerically pure compounds. Second, based upon precedent with closely related secondary alkoxide complexes $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(OCH(CH_3)R)$,[11] it should be possible to recover and recycle the rhenium byproduct $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(Cl)$ from the reactions of (+)-(*RS*)-**3a–e** and MTPA-Cl. However, alternative alkoxide ligand cleavage protocols have been developed that afford configurationally stable neutral carboxylate complexes $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(O(C{=}O)R)$—or even cationic aldehyde and ketone complexes **1** and **2**—in high chemical and optical yields.[8,11] These are superior to the MTPA-Cl methodology, which was selected for exploratory work primarily as a means of assaying addition stereochemistry.

To our knowledge, **3a–e** and **5a–e** constitute the first transition-metal cyanohydrin alkoxides to be isolated. Their stabilities markedly contrast with those of alkali metal cyanohydrin alkoxides. The latter have been identified from rate data as reaction intermediates and rapidly fragment to alkali metal cyanides and aldehydes or ketones.[22] However, many silylated cyanohydrin alkoxides have been isolated.[23]

Although the mechanisms of diastereoselection in Schemes II and III are currently under study,[24] a brief preliminary analysis is informative. It has been previously

Scheme IV. The Most Probable π and σ Cyanide Addition Transition States Give the Same Product Diastereomer



shown that monosubstituted alkene complexes $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(H_2C{=}CHR)]^+ BF_4^-$ are attacked by carbon nucleophiles exclusively upon the C=C face opposite to the rhenium.[25] Accordingly, the configurations of the dominant diastereomers of **3a–e** are consistent with cyanide attack upon the more stable π diastereomers of aldehyde complexes **1a–e** (Scheme I) from a direction opposite to the rhenium. Importantly, the more stable π diastereomers nest the larger alkyl C=O substituent near the smaller nitrosyl ligand and the smaller hydrogen C=O substituent near the larger cyclopentadienyl ligand.

Next, note that methyl ketone complexes **2b–e** can exist as *E*/*Z* (cis/trans) C=O geometric isomers (Scheme I). Although the smaller methyl C=O substituent should prefer to be cis to the bulky rhenium fragment I, quantitative equilibrium data are not presently available. However, based upon measurements with imines of methyl ketones, *E*/*Z* ratios for **2b–d** should be ≥80:20, ≥95:5, and ≥99:1, respectively.[26] Accordingly, the configurations of the dominant diastereomers of **5b–e** are consistent with cyanide attack upon the more stable *E* geometric isomers of **2b–e** from a direction opposite to the bulky PPh_3 ligand.

Although the preceding analyses may seem intuitively satisfying, several caveats deserve emphasis. First, appropriately substituted aromatic aldehyde complexes $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(O{=}CHAr)]^+ BF_4^-$ have been found to exist as mixtures of π and σ isomers.[27] As would be expected, a crystal structure of a σ isomer shows the small hydrogen C=O substituent to be cis to the rhenium. Importantly, π/σ interconversion rates are extremely rapid.[9] Furthermore, α-chloro and α-fluoro derivatives of acetone complex **2a** give appreciable quantities of π isomers.[28] Thus, complexes that exist as π ground states might undergo addition via σ transition states or vice versa.

Scheme IV depicts the more stable π and σ isomers of aldehyde complexes **1**, with L and S representing the larger

(22) (a) Ching, W.-M.; Kallen, R. G. *J. Am. Chem. Soc.* **1978**, *100*, 6119. (b) Ogata, Y.; Kawasaki, A. In *The Chemistry of the Carbonyl Group*; Zabicky, J., Ed.; Wiley: New York, 1970; Vol 2, pp 21–32.
(23) Weber, W. P. *Silicon Reagents in Organic Synthesis*; Springer-Verlag: New York, 1983; Chapter 2.
(24) Klein, D. P. Unpublished results, University of Utah.
(25) Peng, T.-S.; Gladysz, J. A. *Tetrahedron Lett.* **1990**, *31*, 4417.
(26) McGarty, C. G. In *The Chemistry of the Carbon-Nitrogen Double Bond*; Patai, S., Ed.; Wiley: New York, 1970; p 376.
(27) Quirós Méndez, N.; Arif, A. M.; Gladysz, J. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1473.
(28) Klein, D. P.; Dalton, D. M.; Quirós Méndez, N.; Arif, A. M.; Gladysz, J. A. *J. Organomet. Chem.* **1991**, *410*, C7.

alkyl and smaller hydrogen C=O substitutents. Cyanide addition as outlined above clearly leads to the *same* diastereomer of **3** in each case. Alternatively, switching S to a methyl substituent gives the more stable π and σ isomers of methyl ketone complexes **2**. It is again apparent that cyanide addition to either isomer will give identical diastereomers of **5**. Thus, product stereochemistry does not distinguish π and σ addition mechanisms. However, several types of rate experiments suggest that σ isomers of aromatic aldehydes are more reactive toward nucleophiles than π isomers.[24]

Regardless, the diastereoselectivities in Schemes II and III generally increase as the size differences between the C=O substituents increase. This trend is a logical consequence of either mechanism. The diastereoselectivities for cyanide addition to **2b–e** are quite close to those found previously for hydride additions utilizing $K(s\text{-}C_4H_9)_3BH$.[11] However, the diastereoselectivities for cyanide addition to **1a–e** are slightly lower than those obtained for deuteride additions utilizing the racemic chiral deuteroformyl complex $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(CDO)$.[8] This might be due to the reduced bulk of the attacking nucleophile or stereoselectivity-enhancing nonlinear effects that have been documented for the chiral formyl reductant.[8]

In summary, carbon nucleophiles of the formula $^-C{\equiv}X$ have been shown to add to the carbonyl groups of aldehyde and ketone complexes **1** and **2** with good to high yields and diastereomeric excesses. Efforts are currently being directed at the enhancement of these diastereoselectivities, the elucidation of the mechanism of diastereoselection, and the development of methodology that is catalytic in rhenium.

Experimental Section

General Data. Instrumentation, general procedures, and solvent purifications were identical with those described in previous papers,[8,11] with the following additions: mass spectra were obtained on a VG 7070E spectrometer; $(CH_3CH_2)_4N^+\ CN^-$ (Fluka) was used as received; Florisil was treated with concentrated NH_4OH (30% v/w).

$(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(OCH(CN)R)$ (3). Standard Procedures. A. A Schlenk flask was charged with $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(\eta^2\text{-}O{=}CHCH_3)]^+\ BF_4^-$ (**1a**; 150 mg, 0.222 mmol)[8] and CH_2Cl_2 (3 mL) and was cooled to −80 °C. Then $(CH_3CH_2)_4N^+CN^-$ (37 mg, 0.237 mmol) was added and the mixture was stirred at −80 °C for 16 h. Solvent was removed under vacuum, and the residue extracted with C_6H_6 (4 mL). The extract was passed through a 2 × 4 cm Florisil column. The red-orange band was eluted with additional C_6H_6 (10 mL) and solvent removed from the eluate under vacuum. This gave (*RS,SR*)-**3a** as a red-orange foam (0.119 g, 0.193 mmol, 87%).[29] Anal. Calcd for $C_{26}H_{24}N_2O_2PRe$: C, 50.89; H, 3.94; N, 4.56. Found: C, 50.79; H, 3.98; N, 4.52. **B.** Complex (+)-(*RS*)-**1a** (150 mg, 0.222 mmol)[8] and $(CH_3CH_2)_4N^+\ CN^-$ (37 mg, 0.237 mmol) were analogously reacted. An identical workup gave (+)-(*RS*)-**3a** as a red-orange foam (116 mg, 0.189 mmol, 85%).[29] MS:[30] 614 (M^+, 94), 544 ($(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)^+$, 68), 279 ($PPh_3^+$, 100).

Complexes **3b–e** and (+)-(*RS*)-**3b–e** were isolated as red-orange foams by similar procedures. **3b** (from **1b**, 150 mg, 0.218 mmol), 120 mg, 0.192 mmol, 88%.[29] Anal. Calcd for $C_{27}H_{26}N_2O_2PRe$: C, 51.66; H, 4.18; N, 4.46. Found: C, 51.56; H, 4.21; N, 4.40. (+)-(*RS*)-**3b** (from (+)-(*RS*)-**1b**, 150 mg, 0.218 mmol), 126 mg, 0.201 mmol, 92%.[29] MS: 628 (M^+, 89), 544 ($(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)^+$, 100). **3c** (from **1c**, 150 mg, 0.213 mmol), 123 mg, 0.191 mmol, 90%.[29] Anal. Calcd for $C_{28}H_{28}N_2O_2PRe$: C, 52.41; H, 4.40; N, 4.37. Found: C, 52.46; H, 4.43; N, 4.34. (+)-(*RS*)-**3c** (from (+)-(*RS*)-**1c**, 150 mg, 0.214 mmol), 127 mg, 0.198 mmol, 93%.[29] MS: 642 (M^+, 100), 544 ($(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)^+$, 96). **3d** (from **1d**, 150 mg, 0.200 mmol), 116 mg, 0.169 mmol, 85%.[29] A sample was crystallized from toluene/hexanes. Anal. Calcd for $C_{32}H_{28}N_2O_2PRe$: C, 55.72; H, 4.09; N, 4.06. Found: C, 55.80; H, 4.27; N, 4.32. (+)-(*RS*)-**3d** (from (+)-(*RS*)-**1d**, 150 mg, 0.200 mmol), 113 mg, 0.163 mmol, 78%; corrected for a ca. 4% impurity, ^1H NMR: δ 4.59.[29] MS: 690 (M^+, 100), 544 ($(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)^+$, 95), 279 ($PPh_3^+$, 38). **3e** (from **1e**, 150 mg, 0.204 mmol), 128 mg, 0.189 mmol, 93%.[29] A sample was crystallized from toluene/hexanes. Anal. Calcd for $C_{31}H_{26}N_2O_2PRe$: C, 55.10; H, 3.88; N, 4.15. Found: C, 55.45; H, 3.88; N, 3.94. (+)-(*RS*)-**3e** (from (+)-(*RS*)-**1e**, 150 mg, 0.204 mmol), 134 mg, 0.199 mmol, 97%.[29] MS: 676 (M^+, 1), 279 (PPh_3^+, 100).

$(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(OCCH_3(CN)R)$ (5). Standard Procedure. A Schlenk flask was charged with $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(\eta^1\text{-}O{=}C(CH_3)_2)]^+\ BF_4^-$ (**2a**; 29 mg, 0.042 mmol)[11] and CH_2Cl_2 (3 mL) and was cooled to −80 °C. Then $(CH_3CH_2)_4N^+\ CN^-$ (7 mg, 0.045 mmol) was added with stirring and the solution was allowed to slowly warm to 0 °C over a 5 h period. Solvent was removed under vacuum and the residue was extracted with C_6H_6. The extract was filtered through a 2 × 2 cm CaO column, and the solvent was removed under vacuum to give **5a** as a red-orange foam (16 mg, 0.025 mmol, 60%). MS:[30] 628 (M^+, 69), 544 ($(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)^+$, 100).

Complexes **5b–e** were isolated as orange foams or powders by similar procedures. **5b** (from **2b**, 56 mg, 0.080 mmol), 36 mg, 0.056 mmol, 70%.[29] MS: 642 (M^+, 12), 544 ($(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)^+$, 100). **5c** (from **2c**, 26 mg, 0.036 mmol), 20 mg, 0.030 mmol, 79%.[29] MS: 656 (M^+, 60), 544 ($(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)^+$, 100). **5d** (from **2d**, 29 mg, 0.040 mmol), 20 mg, 0.030 mmol, 75%.[29] MS: 670 (M^+, 13), 544 ($(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)^+$, 100). **5e** (from **2e**, 25 mg, 0.033 mmol), 20 mg, 0.029 mmol, 88%.[29] MS: 690 (M^+, 3), 544 ($(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)^+$, 100).

$(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(OCCH_3(C{\equiv}CSi(CH_3)_3)C_6H_5)$ (6). A Schlenk flask was charged with **2e** (51 mg, 0.068 mmol) and THF (10 mL) and was cooled to −80 °C. Then $(CH_3)_3SiC{\equiv}CLi$ (0.1 M in THF, 0.840 mL, 0.084 mmol)[31] was added dropwise with stirring. The mixture was allowed to slowly warm to room temperature and worked up in a procedure similar to that given for **5a**. This gave (*RS,SR*)-**6** as an orange oily solid (46 mg, 0.060 mmol, 88%).[29] Salmon polymorphous crystals were obtained from toluene/pentane (−20 °C). Anal. Calcd for $C_{36}H_{37}NO_2PReSi$: C, 56.80; H, 4.99; Si, 3.80. Found: C, 56.90; H, 4.98; Si, 4.07.

$C_6H_5(CH_3O)(F_3C)CC(=O)OCH(CN)R$ (4). Standard Procedure. A round-bottom flask was charged with (+)-(*RS*)-**3a** (89 mg, 0.143 mmol),[29] DMAP (18 mg, 0.143 mmol), and C_6H_6 (2 mL). Then (−)-$C_6H_5(CH_3O)(F_3C)CC(=O)Cl$ (MTPA-Cl; 0.053 mL, 0.283 mmol) was added dropwise and the resulting suspension stirred for 15 h. The mixture was filtered through a 4 × 2 cm column of $AgNO_3$-impregnated silica gel (15% w/w), which was eluted with additional benzene (15 mL).[32] The eluate was concentrated and chromatographed on silica gel using ethyl acetate/hexane (100 mL 2:98 v/v, then 80 mL, 10:90 v/v). Ester-containing fractions (assayed by capillary GLC, 25 × 0.20 mm SE-54, 170 → 200 °C at 5 °C/min)[33] were combined, and solvent was removed to give (*SS*)-**4a** (39 mg, 0.137 mmol, 96%)[29] as a light yellow oil.

Compounds (*SS*)-**4b–e** were similarly obtained as light yellow oils as follows. (+)-(*RS*)-**3b** (81 mg, 0.130 mmol), DMAP (16 mg, 0.128 mmol), and (−)-MTPA-Cl (0.048 mL, 0.260 mmol) gave (*SS*)-**4b** (36 mg, 0.121 mmol, 93%).[29] (+)-(*RS*)-**3c** (96 mg, 0.149 mmol), DMAP (19 mg, 0.152 mmol), and (−)-MTPA-Cl (0.056 mL, 0.299 mmol) gave (*SS*)-**4c** (44 mg, 0.141 mmol, 94%;[29] corrected for $(MTPA)_2O$ byproduct, ca. 15% by weight). (+)-(*RS*)-**3d** (80 mg, 0.117 mmol), DMAP (14 mg, 0.116 mmol), and (−)-MTPA-Cl (0.043 mL, 0.233 mmol) gave previously characterized[5c] (*SS*)-**4d** (36 mg, 0.100 mmol, 85%).[29] (+)-(*RS*)-**3e** (95 mg, 0.141 mmol), DMAP (17 mg, 0.141 mmol), and (−)-MTPA-Cl (0.052 mL, 0.282 mmol) gave previously characterized[6a] (*SS*)-**4e** (43 mg, 0.122 mmol, 87%).[29]

(29) For diastereomeric purity, see Schemes II and III and eq 1.
(30) Conditions: (+)-FAB, 7kV, Ar, 3-nitrobenzyl alcohol/chloroform matrix, m/z (relative intensity), ^{187}Re.
(31) Wulff, W. D.; Tang, P.-C.; Chan, K.-S.; McCallum, J. S.; Yang, D. C.; Gilbertson, S. R. *Tetrahedron* **1985**, *41*, 5813.
(32) This step removes the byproduct $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(Cl)$.
(33) The major diastereomers (*SS*)-**4a–e** elute from the GLC column before (*SR*)-**4a–e**. Also, the diastereomers fractionate slightly on silica gel.

Selected data. IR (cm^{-1}, neat): 1762–1763 (vs), 1174 (vs). ^1H NMR (δ, C_6D_6; HCCN and OCH_3 resonances): (*SS*)/(*SR*)-**4a**, 4.75/4.68 (q, J_{HH} = 7.0 Hz), 3.30/3.20 (q, J_{HF} = 1.2 Hz); (*SS*)/(*SR*)-**4b**, 4.77/4.69 (t, J_{HH} = 6.5 Hz), 3.32/3.22 (q, J_{HF} = 1.2 Hz); (*SS*)/(*SR*)-**4c**, 4.82/4.74 (d, J_{HH} = 5.7 Hz), 3.34/3.24 (q, J_{HF} = 1.2 Hz); (*SS*)/(*SR*)-**4d**, 5.17/5.10 (dd, J_{HH} = 7.3/6.1 Hz), 3.25/3.06 (q, J_{HF} = 1.2 Hz); (*SS*)/(*SR*)-**4e**, 6.04/6.03 (s), 3.31/3.16 (q, J_{HF} = 1.2 Hz).

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Supplementary Material Available: Complete IR, NMR (^1H, ^{13}C), and mass spectroscopic data for (*SS*)-**4a–e** and partial data for (*SR*)-**4a–e** in tabular format (4 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Clavukerin A: A New Trinorguaiane Sesquiterpene. Biomimetic Synthesis of (±)-Clavularin A from (±)-Clavukerin A

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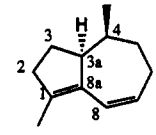
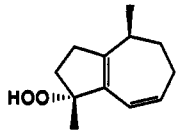
(±)-Clavukerin A, 2,8-dimethylbicyclo[5.3.0]deca-5,7-diene, was first synthesized utilizing thermal [2 + 2] cycloaddition and two carbon ring expansion reactions as key elements. (±)-Clavukerin A was transformed, via photooxidation mimicking the biogenetic reaction, into (±)-clavukerin C, which was further rearranged into (±)-clavularin A by acid catalysis.

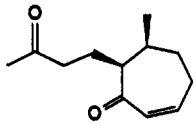
(−)-Clavukerin A, an unstable trinorguaiane sesquiterpene, was first isolated by the Kitagawa[1] group from the Okinawan soft coral, *Clavularia koellikeri*, along with (−)-clavukerin C. Its structure was deduced by spectral and chemical analysis in addition to X-ray crystallography of its diepoxide derivative as (1*S*,2*S*)-2,8-dimethylbicyclo[5.3.0]deca-5,7-diene. From the same coral the Endo group[2] isolated the cytotoxic (−)-clavularins A and B, which were assumed to be derived from (−)-clavukerin C either biogenetically or secondarily during the isolation of the unstable (−)-clavukerin C. Later the Kitagawa group obtained (−)-clavularin A and (−)-clavukerin C from (−)-clavukerin A by chemical oxidation (with $OsO_4/NaIO_4$) and photooxidation[1], respectively. Recently syntheses of (±)-clavularin A and (±)-clavularin B have been reported.[3,4]



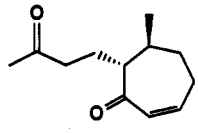
(-)-Clavukerin A



(-)-Clavukerin C



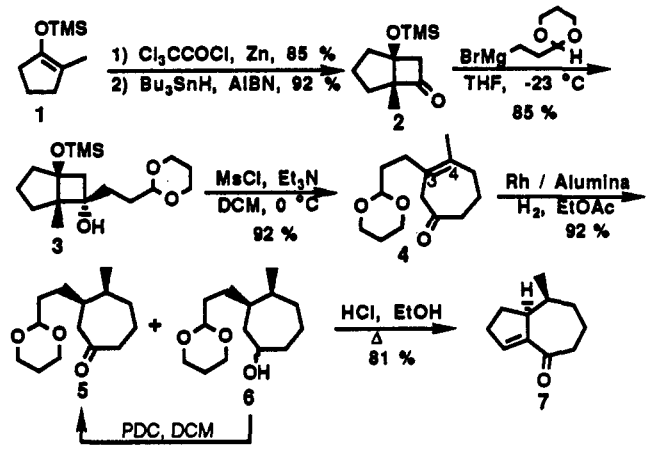
(-)-Clavularin A



(-)-Clavularin B

Here we report our efficient approach to the first total synthesis of (±)-clavukerin A employing our previously reported[5] methodology for the formation of substituted β,γ-unsaturated cycloheptenones. As a preliminary study

Scheme I



before the synthesis of (±)-clavukerin A, we undertook the preparation of enone **7**, which has the same trans configuration[6] between the C-3a proton and C-4 methyl as (±)-clavukerin A (Scheme I). A similar synthetic strategy, which involves fusion of the five-membered ring onto a preexisting cycloheptane ring, was first used by Heathcock[7] for the synthesis of the hydroazulene ring system. However, our approach has the distinctive feature that the side chain attachment to the β,γ-unsaturated cycloheptenone was easily accomplished through our method and highly selective stereochemical control of the relative configuration of the C-3 and C-4 substituents was possible via catalytic hydrogenation. Silyl enol ether **1** of 2-methylcyclopentanone was converted to bicyclic ketone **2** according to a known procedure.[5] Addition of the Grignard reagent of 2-(2-bromoethyl)-1,3-dioxane in THF at −23 °C to ketone **2** afforded exclusively endo alcohol **3** in 85% yield.

(1) (a) Kobayashi, M.; Son, B. W.; Kido, M.; Kyogoku, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1983**, *31*, 6. (b) Kobayashi, M.; Son, B. W.; Kyogoku, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1984**, *32*, 1667. (c) Numbering of the clavukerins and related compounds throughout this paper is based on the hydroazulene ring system.

(2) Endo, M.; Nakagawa, M.; Hamamoto, Y.; Nakanishi, T. *J. Chem. Soc., Chem. Commun.* **1983**, 322.

(3) Still, I. W.; Shi, Y. *Tetrahedron Lett.* **1987**, 2489.

(4) Urech, R. *J. Chem. Soc., Chem. Commun.* **1984**, 989.

(5) Pak, C. S.; Kim, S. K. *J. Org. Chem.* **1990**, *55*, 1954.

(6) The terms cis and trans in this paper refer to the relationship between the C-3a proton and C-4 methyl of the hydroazulene nucleus.

(7) (a) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley-Interscience: New York, 1983; Vol. 5, pp 333–390 and references cited therein. (b) Heathcock, C. H.; Tice, C. M.; Germroth, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 6081. (c) Heathcock, C. H.; DelMar, E. G.; Graham, S. L. *J. Am. Chem. Soc.* **1982**, *104*, 1907.

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