Synthesis of Trans Olefins by a Nickel-Catalyzed Reduction of Enol Ethers. A Formal, Total Synthesis of (±)-Recifeiolide

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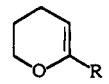
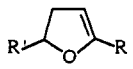
Some time ago it was shown that the interaction of enol ethers with Grignard reagents, catalyzed by low-valent nickel species, led to replacement of the alkoxy groups by alkyl or aryl units, creating olefins with retention of configuration.[2] When cyclic enol ethers were used in this reaction, cis olefins were formed,[2c,d,3] a procedure which has been applied to the synthesis of pheromones.[2c,d] It now became of interest to utilize the same enol ethers, e.g., dihydropyran (**1a**) or dihydrofuran (**2a**), for trans olefin formation. It was envisaged that α-lithiation of these enol ethers, alkylation of the resultant lithio compounds,[4] and reduction of the alkylated enol ethers (**1** and **2**, R = alkyl) with Grignard reagents under nickel catalysis (following early leads[2c,d,3a]) would accomplish this task. Furthermore, it was hoped to apply the results to the synthesis of a natural product.



1a, R = H
b, R = *n*-Bu



2a, R = R' = H
b, R = *n*-Bu, R' = H
c, R = *n*-Oct, R' = H
d, R = H, R' = Me
e, R = $(CH_2)_6C(OCH_2)_3CMe$, R' = Me

The enol ether models were 6-*n*-butyl-3,4-dihydro-2*H*-pyran (**1b**),[5] prepared by treatment of dihydropyran (**1a**) with *tert*-butyllithium and thereafter with *n*-butyl iodide, and 5-*n*-butyl-2,3-dihydrofuran (**2b**),[6] prepared from dihydrofuran (**2a**) by the same procedure.[7] In analogy with the nickel-catalyzed reduction of thioenol ethers with Grignard reagents[8] it was hoped to use cyclohexylmagnesium or isopropylmagnesium bromide as the reducing agent. When, however, early experiments showed enol ether **1b** to be inert toward cyclohexylmagnesium bromide,[9] all subsequent tests were carried out only with isopropylmagnesium bromide as the reducing agent. Furthermore, the use of ether solvents resulted in higher product yields than the utilization of aromatic solvents. Finally, tri-*n*-butylphosphine (tbp) proved to be a more efficient ligand (especially when used as a nickel complex in more than catalytic quantity) than the traditionally employed triphenylphosphine (tpp).

Table I. Nickel-Catalyzed Reductions of Enol Ethers 1b and 2b with Isopropylmagnesium Bromide[a]

ether	$NiCl_2$ ligand	solvent	*E*/*Z* ratio	yield (%)
1b[b]	tbp[c]	THF	>25:1	60
1b	tbp	THF	20:1	50
1b	tbp	benzene	10:1	40
1b	tbp	benzene	10:1	35
2b	tbp	THF	10:1	70
2b	tbp	dioxane	6:1	70
2b	tbp	benzene	6:1	40
2b[d]	tpp[e]	benzene	4:1	35

[a] At the temperature of the refluxing solvent; **1b** reaction time 20 h; **2b** reaction time 2 h; 20% $(tbp)_2NiCl_2$ or $(tpp)_2NiCl_2$ catalyst. [b] Reaction time: 48 h. [c] 40% $(tbp)_2NiCl_2$ catalyst. [d] Reaction time: 20 h. [e] 10% $(tpp)_2NiCl_2$ catalyst.

As Table I indicates, the **1b**-derived products were 4*E* (**3a**)[10] and 4*Z* (**4a**)[2d,e,10e–g,11] isomers of 4-nonen-1-ol and the **2b**-emanating substances 3*E* (**3b**)[10b,g,12] and 3*Z* (**4b**)[2e,10g,13] isomers of 3-octen-1-ol. The major product of all reactions was the trans olefin, the trans/cis ratio varying from 4:1 to >25:1.[14] Furthermore, it could be shown that the annoying presence of *Z*-olefins as minor components of the reduction mixtures may be the consequence of a postreduction isomerization process. Thus, for example, exposure of pure **3b** to the reaction conditions (benzene, $(tpp)_2NiCl_2$) of the reduction of dihydrofuran **2b** yielded a **3b**–**4b** mixture in the same ratio as in the earlier reduction (no structure change taking place without nickel catalyst).

With the above data in hand it now was possible to undertake the synthesis of a naturally occurring substance containing a trans double bond, and the fungal metabolite

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(7) 5-*n*-Octyl-2,3-dihydrofuran (**2c**) [colorless liquid; ^1H NMR δ 0.8–0.9 (m, 3, Me), 1.37 (m, 12, methylenes) 2.11, 2.58 (t, 2 each, J = 8 Hz, allyl Hs), 4.30 (t, 2, J = 8 Hz, OCH_2), 4.58 (t, 1, J = 1 Hz, H-4)] served as a third model.

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(9) In one experiment [**1b** + *c*-HexMgBr + 20% $[(C_6H_5)_3P]_2NiCl_2$ in benzene being refluxed for 20 h] there was obtained a 9:1 **3a**–**4a** mixture in 10% yield.

(10) (a) Paul, R.; Riobé, O. C. R. *Acad. Sci.* **1947**, *224*, 474. (b) Crombie, L.; Harper, S. H. *J. Chem. Soc.* **1950**, 1707. (c) Ansell, M. F.; Thomas, D. A. *J. Chem. Soc.* **1957**, 3302. (d) Pattison, F. L. M.; Dear, R. E. A. *Can. J. Chem.* **1963**, *41*, 2600. (e) Bestmann, H. J.; Koschatzky, K. H.; Stransky, W.; Vostrowsky, O. *Tetrahedron Lett.* **1976**, 353. (f) Ohloff, G.; Vial, C.; Näf, F.; Pawlak, M. *Helv. Chim. Acta* **1977**, *60*, 1161. (g) Bestmann, H. J.; Koschatzky, K. H.; Schätzke, W.; Süsz, J.; Vostrowsky, O. *Liebigs Ann. Chem.* **1981**, 1705. (h) Evans, D. A.; Thomas, E. W.; Cherpeck, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 3695.

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(13) (a) Disselnkötter, H.; Eiter, K.; Karl, W.; Wendisch, D. *Tetrahedron* **1976**, *32*, 1591. (b) Crandall, J. K.; Collonges, F. *J. Org. Chem.* **1976**, *41*, 4089. (c) Alexakis, A.; Cahiez, G.; Normant, J. F. *Tetrahedron* **1980**, *36*, 1961.

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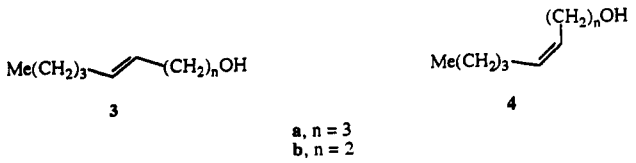
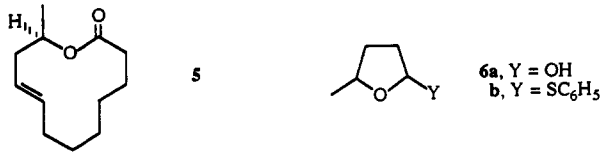
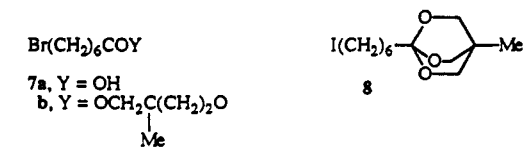


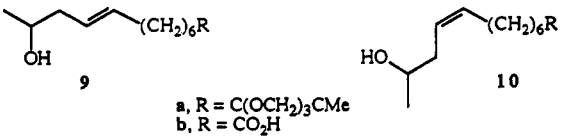
recifeiolide (**5**)[15] was chosen for this purpose.[16] Furthermore, in order to apply the above organometallic reaction to its synthesis, a dihydrofuran based on 2-methyl-2,3-dihydrofuran (**2d**) and a masked ω-haloenanthic acid derivative had to be constructed. Hence the following transformations were executed.



Exposure of 5-methyl-2-tetrahydrofuranol (**6a**), prepared by the reduction of γ-valerolactone with diisobutylaluminum hydride,[17] to thiophenol and boron trifluoride etherate yielded the THF derivative **6b**.[17] Pyrolysis of the latter in the presence of DBU yielded the desired dihydrofuran **2d**.[17b,18] Sequential treatments of 7-bromoheptanoic acid (**7a**)[19] with thionyl chloride and 3-(hydroxymethyl)-3-methyloxetane[20] produced bromo ester **7b**, whose interaction with sodium iodide in acetone and thereafter with boron trifluoride etherate[20,21] furnished an ω-iodoorthoenanthate **8**.



When enol ether **2d** was metalated[4] with *tert*-butyllithium and the α-lithio derivative of **2d** exposed to iodide **8**, the product was dihydrofuran **2e**, the substrate needed for the above organonickel chemistry. Reduction of the enol ether **2e** with isopropylmagnesium bromide in the presence of $(tbp)_2NiCl_2$ in refluxing THF for 20 h led in 48% yield to a 4:1 mixture of orthoesters **9a** and **10a**,[22] whose mild acid hydrolysis afforded a mixture (95%) of hydroxy acids **9b** and **10b**. Purification of the major component after lactonization[16a] of the mixture furnished (±)-recifeiolide (**5**) in 50% yield.



Experimental Section

General. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded at 200 and 50.31 MHz, respectively. IR spectra were recorded of CCl_4 solutions; mass spectra were obtained in the chemical ionization mode. GC product analysis was performed with a 50-m capillary Carbowax 20M column.

Bis(tri-*n*-butylphosphino)nickel Dichloride [$(tbp)_2NiCl_2$]. The complex was prepared according to the published procedure,[23] modified as follows. Tri-*n*-butylphosphine (20 mL, 80 mmol) was added to a stirring solution of 9.52 g (40 mmol) of $NiCl_2 \cdot 6H_2O$ in 35 mL of 70% aqueous alcohol at 5 °C, and the stirring of the now red mixture was continued for 0.5 h. The red precipitate was filtered, washed with ice-cold ethanol, and dried under vacuum. This led to 20.0 g (94%) of the catalyst.

6-*n*-Butyl-3,4-dihydro-2*H*-pyran (1b). A 1.7 M *t*-BuLi solution (32 mL, 52 mmol) was added dropwise to a stirring solution of 4.3 mL (48 mmol) of dihydropyran (**1a**) in 16 mL of anhydrous THF under argon at −60 °C and the temperature then permitted to rise to 5 °C. A solution of 5 mL (48 mmol) of *n*-butyl iodide in 5 mL of anhydrous THF was added dropwise to the stirring mixture at −30 °C. The mixture was allowed to warm to rt and the stirring under argon continued for 2 h. A saturated NH_4Cl solution (6 mL) was added slowly and the mixture extracted with ether. The extract was dried (Na_2SO_4) and evaporated. Distillation (60–65 °C (0.5 Torr)) of the residue furnished 6.4 g (95%) of colorless, liquid ether **1b**, IR and ^1H NMR spectrally identical with recorded data.[5]

5-*n*-Butyl-2,3-dihydrofuran (2b).[6] The literature procedure was used for the **2a** → **2b** conversion. Since distillation decomposed the product, it has to be used in the next reaction without further purification: IR C=C 1670 (w) cm^{-1}; ^1H NMR δ 0.90 (t, 3, J = 7 Hz, Me), 1.3–1.6, 1.9–2.2, 2.5–2.7 (m, 8, methylenes), 4.29 (t, 2, J = 8 Hz, OCH_2), 4.5–4.6 (m, 1, H-4); ^{13}C NMR δ 13.7 (Me), 22.2, 27.4, 28.7, 29.8 (methylenes), 69.5 (C-2), 93.3 (C-4), 158.9 (C-5).

4(*E*)-Nonen-1-ol (3a). A solution of 1.9 mL (20 mmol) of freshly distilled 2-bromopropane in 10 mL of anhydrous THF was induced to interact with 480 mg (20 mmol) of magnesium turnings, furnishing 19 mmol of Grignard solution (76%). The titrated solution of the Grignard reagent was added dropwise to a solution of 1.06 g (2.0 mmol, 0.4 equiv) of $(tbp)_2NiCl_2$ in 30 mL of dry THF. Enol ether **1b** (0.70 g, 5 mmol) was added slowly, and thereafter the mixture was stirred and refluxed under argon for 48 h. Saturated NH_4Cl was added slowly under vigorous stirring. The mixture was extracted with ether and the extract dried. Evaporation yielded 430 mg (60%) of alcohol **3a** (>96% *E*-isomer by GC): bp 110 °C (12 Torr); ^1H NMR spectrally identical with recorded data.[10]

The *Z* isomer (**4a**, <4%) was identified by GC and spectrally.[2e]

3(*E*)-Octen-1-ol (3b). The same procedure, except for the use of 20% catalyst and 2 h reaction time, applied to dihydrofuran

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(22) The apparent lowering of the *E*/*Z* product ratio with increasing length of the side chain was accord with the difference in the ratios of the reduction products of the butylated dihydrofuran **2b** (10:1, see the table) vs the octylated heterocycle **2c**[7] (4:1).

(23) Jensen, K. A. *Z. Anorg. Allgem. Chem.* **1936**, *229*, 265.

2b gave a 70% yield of alcohol **3b** (>91% *E* isomer by GC): bp 106 °C (12 Torr); NMR spectrally identical with recorded data.[10b,g,12]

The *Z* isomer (**4b**) was identified by GC and spectrally.[2e]

2-Methyl-2,3-dihydrofuran (2d). A mixture of 14.0 g (72 mmol) of sulfide **6b** and 12.2 g (80 mmol) of DBU was heated in a distillation apparatus at 250 °C until all distillation ceased. The distillate was redistilled, and the fraction boiling below 100 °C was collected. Redistillation of this fraction gave 4.00 g (66%) of enol ether **2d**: bp 64–66 °C; IR and ^{1}H NMR spectrally identical to reported data;[18] ^{13}C NMR δ 21.6 (Me), 36.2 (C-3), 77.5 (C-2), 99.7 (C-4), 144.6 (C-5).

1-Methyl-3-oxacyclobutanecarbinyl 7-Bromoheptanoate (7b). A mixture of 7.00 g (33.6 mmol) of 7-bromoheptanoic acid (**7a**)[19] and excess (6 mL, 69 mmol) of $SOCl_2$ was stirred at 5 °C for 12 h. The excess reagent was removed by distillation under reduced pressure and the residue diluted with 5 mL of anhydrous THF. The resultant solution was added dropwise to a stirring mixture of 4.00 g (39 mmol) of 3-(hydroxymethyl)-3-methyloxetane[20] and 4.5 mL of pyridine in 35 mL of dry THF at 5 °C. After 1.5 h the mixture was poured into saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was dried and evaporated, yielding 9.50 g (97%) of crude ester **7b**, used in the next step without further purification. For full characterization 500 mg of **7b** was exposed to flash chromatography on silica gel. Elution with 4:1 hexane–ethyl acetate led to 460 mg (89%) of colorless, liquid ester **7b**: IR C=O 1738 (s) cm^{-1}; ^{1}H NMR δ 1.2–2.0 (m, 8, methylenes), 1.33 (s, 3, Me), 2.37 (t, 2, J = 7 Hz, $COCH_2$), 3.40 (t, 2, J = 7 Hz, $BrCH_2$), 4.18 (s, 2, CO_2CH_2), 4.39, 4.55 (d, 2 each, J = 6 Hz, OCH_2), ^{13}C NMR δ 20.8 (Me), 24.3, 27.4, 27.8, 32.1 (methylenes), 33.3 (α-keto-CH_2, or $BrCH_2$), 33.6 ($BrCH_2$ or α-keto-CH_2), 38.7 (C-3), 66.0 (OCH_2), 79.1 (C-2), 173.1 (C=O). Anal. Calcd for $C_{12}H_{21}O_3Br$: C, 49.16; H, 7.22. Found: C, 48.95; H, 7.29.

1-(6-Iodohexyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (8). A solution of 9.00 g (30.7 mmol) of bromo ester **7b** and 10 g (67 mmol) of NaI in 60 mL of acetone was stirred under nitrogen for 4 h. The mixture was filtered, and the filtrate was concentrated by evaporation and poured into water. The aqueous solution was extracted with CH_2Cl_2 and the extract washed with brine solution, dried, and evaporated. Flash chromatography of the residue (9.8 g) on silica gel and elution with 4:1 hexane–ethyl acetate furnished 9.10 g (88% from crude **7b**, 80% from **7a**) of colorless, liquid iodo ester (**7b**, I in place of Br): IR C=O 1735 (s) cm^{-1}; ^{1}H NMR δ 1.3–1.9 (m, 4, methylenes), 1.35 (s, 3, Me), 2.39 (t, 2, J = 7 Hz, $COCH_2$), 3.20 (t, 2, J = 7 Hz, ICH_2), 4.18 (s, 2, CO_2CH_2), 4.40, 4.53 (d, 2 each, J = 6 Hz, OCH_2); ^{13}C NMR δ 6.7, 24.4, 27.7, 29.8, 33.0, 33.8 (methylenes), 21.0 (Me), 38.8 (C-3), 68.2 (OCH_2), 79.3 (C-2), 173.3 (C=O). Anal. Calcd for $C_{12}H_{21}O_3I$: C, 42.37; H, 6.22. Found: C, 42.18; H, 6.17.

Conversion of the iodo ester (4.50 g, 13 mmol) into the ortho ester **8** followed the Keinan procedure.[21] Product purification was by flash chromatography, the crude product being placed on the silica column as a 13:1 hexane–triethylamine solution and eluted with the same solvent mixture. This yielded 3.00 g (67%) of colorless, liquid iodide **8**: ^{1}H NMR δ 0.80 (s, 3, Me), 1.2–1.9 (m, 10, methylenes), 3.20 (t, 2, J = 7 Hz, ICH_2), 3.90 (s, 6, 3 OCH_2); ^{13}C NMR δ 6.9, 22.6, 28.0, 30.0, 33.1, 36.2 (methylenes), 14.3 (Me), 29.9 (C-4), 72.2 (C-3, C-5, C-8), 108.6 (C-1). Anal. Calcd for $C_{12}H_{21}O_3I$: C, 42.37; H, 6.22. Found: C, 42.41; H, 6.26.

5-[6-(4′-Methyl-2′,6′,7′-trioxabicyclo[2.2.2]oct-1′-yl)hexyl]-2-methyl-2,3-dihydrofuran (2e). The procedure of the above **2a** → **2b** conversion was applied to 2.2 mL (24 mmol) of dihydrofuran **2d** and 2.95 g (8.7 mmol) of iodide **8**. Chromatography of the crude product (3.4 g) on neutral alumina (activity I) and elution with 9:1 hexane–ethyl acetate afforded 2.25 g (88%) of colorless, liquid enol ether **2e**: IR C=C 1664 (w) cm^{-1}; ^{1}H NMR δ 0.80 (s, 3, Me), 1.2–2.8 (m, 14, 7 CH_2), 1.25 (d, 6, J = 6 Hz, 2-Me), 3.85 (s, 6, 3 OCH_2), 4.3–4.4 (m, 1, H-4), 4.5–4.7 (m, 1, H-2); ^{13}C NMR δ 22.8, 26.2, 27.8, 28.8, 29.0, 36.4, 37.0 (methylenes), 14.3 (4′-Me), 21.7 (2-Me), 29.9 (C-4′), 72.3 (C-3′, C-5′, C-8′), 77.2 (C-2), 92.5 (C-4), 108.8 (C-1′), 157.6 (C-5). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.89; H, 9.59.

(±)-Recifeiolide (5). A freshly prepared 1 M THF solution of isopropylmagnesium bromide (40 mL, 40 mmol) was added dropwise to 540 mg (1.0 mmol) of $(tbp)_2NiCl_2$ in 10 mL of anhydrous THF under argon and the mixture refluxed for 45 min. A solution of 700 mg (2.3 mmol) of dihydrofuran **2e** in 10 mL of dry THF was added dropwise at the elevated temperature and the heating continued for 20 h. A 7:3 aqueous NH_4Cl/NH_3 solution was added to the mixture cooled to 5 °C and stirred for 20 min. The aqueous phase was extracted exhaustively with EtOAc, the extract was dried and evaporated, and the residue was chromatographed on 200 g of alumina. Elution with 10:1 hexane–EtOAc furnished 340 mg (48%) of a 4:1 *E*/*Z* mixture (by GLC and ^{13}C NMR spectral analysis) of liquid hydroxy ortho esters (i.e. **9a** and **10a**). **9a**: IR OH 3610 (w), 3490 (w) cm^{-1}; ^{1}H NMR δ 0.79 (s, 3, Me), 1.1–1.7 (m, 10, methylenes), 1.20 (d, 3, J = 6 Hz, Me), 1.9–2.3 (m, 4, allyl Hs), 3.6–3.9 (m, 1, OCH), 3.85 (s, 6, 3, OCH_2), 5.2–5.6 (m, 2, olefinic Hs); ^{13}C NMR δ 14.4 (Me), 22.5 (Me), 22–42 (methylenes), 67.0 (OCH), 72.4 (OCH_2), 108.9 (O_3C), 125.6 (olefinic C), 134.4 (olefinic C). **10a**: ^{13}C NMR δ 14.4 (Me), 22.6 (Me), 22–42 (methylenes), 67.5 (OCH), 72.4 (OCH_2), 108.9 (O_3C), 124.9 (olefinic C), 133.1 (olefinic C). Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.27; H, 10.17.

A 1:1 DME/H_2O solution of $NaHSO_4$ (3 mL; pH 3) was added to 300 mg (1.0 mmol) of the **9a–10a** ortho ester mixture in 2 mL of DME at 5 °C, and the mixture was stirred for 3 h. A 1 N 3:1 DME/H_2O solution of KOH (6 mL) was added dropwise, and the mixture was stirred at rt for 12 h. The basic solution was acidified with $NaHSO_4$ to pH 2, diluted with water, and extracted exhaustively with CH_2Cl_2. The extract was washed with brine, dried, and evaporated, yielding 204 mg (95%) of a liquid **9b–10b** hydroxy acid mixture. **9b**: IR OH 3608 (w), 3400 (w, br), C=O 1718 (s) cm^{-1}; ^{1}H NMR δ 1.26 (d, 3, J = 7 Hz, Me), 1.3–1.7 (m, 8, methylenes), 1.8–2.3 (m, 4, allyl Hs), 2.3–2.4 (m, 2, $COCH_2$), 3.7–3.9 (m, 1, OCH), 5.3–5.7 (m, 2, olefinic Hs); ^{13}C NMR δ 22.3 (Me), 24–42 (methylenes), 67.4 (OCH), 125.8 (olefinic C), 134.0 (olefinic C), 178.7 (C=O). **10b**: ^{13}C NMR δ 22.4 (Me), 24–42 (methylenes), 67.8 (OCH), 125.1 (olefinic C), 132.7 (olefinic C). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.09; H, 10.47.

The Corey procedure for lactonization[16a] was applied to 100 mg of hydroxy acid mixture **9b–10b**. However, workup consisted of flash chromatography on silica. Elution with 9:1 hexane–EtOAc afforded 45 mg (exclusively pure *E* isomer) of (±)-recifeiolide (**5**), spectrally fully compatible with the published data.[16a]

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