Tandem [4 + 2]/[3 + 2] Cycloadditions of Nitroalkenes. 10. *trans*-2-(1-Methyl-1-phenylethyl)cyclohexanol as a New Auxiliary

Scott E. Denmark* and Atli Thorarensen

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

Received May 17, 1996

The asymmetric variant of the tandem [4 + 2]/[3 + 2] cycloaddition of nitroalkenes with chiral vinyl ethers has been extensively explored in recent years.[1] To date, the chiral vinyl ethers that have been utilized in the tandem sequence are derived from bornane-2,3-diol, **1**, *trans*-2-phenylcyclohexanol, **2**, and 2,2-diphenylcyclopentanol, **3**, Figure 1. These auxiliaries have served admirably in many aspects of the cycloaddition process, but some limitations still exist, such as the following: (1) length of synthesis, (2) low selectivity in exo mode cycloadditions or (3) unavailability in both enantiomeric series.

In the course of a number of total synthesis projects that employ the tandem sequence, we were forced to consider alternatives that addressed some of the limitations noted above.[2] In particular, material through-put became an important issue since the critical unmasking of the nitroso acetals to α-hydroxy lactams involves up to a 50% mass loss due to the size of the chiral auxiliaries employed. Thus, it is of critical importance that the auxiliaries be easily prepared and inexpensive. Comins has recently disclosed the use of an easily prepared auxiliary, *trans*-2-cumylcyclohexanol, **4** (TCC), for the diastereoselective addition of Grignard reagents to alkoxypyridines.[3] The preparation of TCC by Comins is considerably more simple than that previously reported by Whitesell, making this auxiliary an interesting alternative for use in the nitroalkene cycloaddition chemistry.[4]

By analogy with the preparation of the vinyl ethers derived from phenylcyclohexanol, **2,** and 2,2-diphenylcyclopentanol, **3**, the transetherification of **4** with a vinyl ether was explored.[5] TCC is a very sterically crowded auxiliary, since the 1-methyl-1-phenylethane presents a larger steric bulk than the phenyl group in 2-phenylcyclohexanol. Therefore, a higher boiling vinyl ether was required for the trans-etherification. *n*-Butyl vinyl ether was found to be the vinyl ether of choice as was also the case for 2,2-diphenylcyclopentanol.[6] Optimized reaction conditions employed two portions of 0.6 equiv of mercury(II) acetate in a dilute solution of *n*-butyl vinyl ether as solvent, Scheme 1. The vinyl ether, (−)-**5**, was isolated in 62% yield along with 33% of recovered alcohol, (−)-**4**.

To evaluate the utility of this new auxiliary in the tandem [4 + 2]/[3 + 2] cycloaddition, the nitroalkene **6** was selected as the model substrate since it had been used previously with all the other chiral vinyl ethers.[6] Furthermore, it was imperative to deduce the sense of asymmetric induction exercised by this new auxiliary. We, therefore, needed to establish to which enantiomeric series the final α-hydroxy lactam belonged. Accordingly, slow addition of the nitroalkene **6** to a cold solution of methylaluminum bis(2,6-diphenylphenoxide) (MAPh)[7] and vinyl ether (+)-**5** afforded the nitroso acetal **7** in 85% yield, Scheme 2. By ^{1}H NMR analysis of HC(6) the product composition was estimated to be a 145/1.8/1.0 (exo/exo/endo) mixture of diastereomeric nitroso acetals. The major diastereomer was assumed to have a trans relationship between HC(4a) and HC(6) on the basis of the documented preference of MAPh to promote exo-mode [4 + 2] cycloadditions.[8] The nitroso acetal **7** was then unmasked under the standard hydrogenolysis conditions (Raney nickel/1 atm H_2/rt/MeOH). The α-hydroxy lactam, (−)-**8**, isolated in 76% yield (along with an

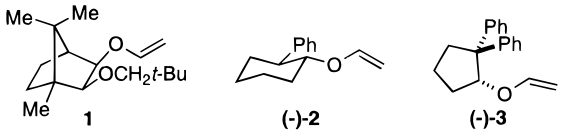
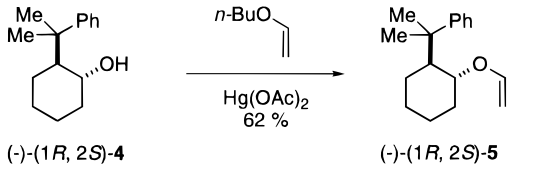
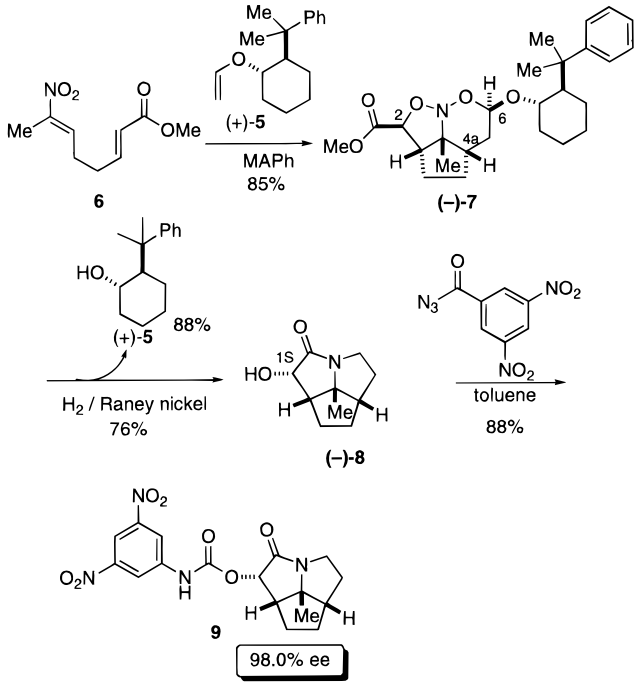


Figure 1. Chiral auxiliaries employed in the tandem [4 + 2]/[3 + 2] cycloadditions of nitroalkenes.

Scheme 1



Scheme 2



(1) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.
(2) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Org. Chem.* **1995**, *60*, 3574.
(3) (a) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656. (b) Comins, D. L.; Salvador, J. M. *Tetrahedron Lett.* **1993**, *34*, 801. (c) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1994**, *35*, 7343.
(4) Whitesell, J. K.; Lawrence, R. M. *Chimia* **1986**, *40*, 318.
(5) The vinyl ether of phenmenthol has been prepared earlier in a two-step procedure, by the preparation of the acetylenic ether followed by a partial reduction. Denmark, S. E.; Senanayake, C. B. W.; Ho, G. D. *Tetrahedron* **1990**, *46*, 4857.
(6) (a) Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1859. (b) Denmark, S. E.; Schnute, M. E.; Marcin, L. R.; Thorarensen, A. *J. Org. Chem.* **1995**, *60*, 3205.
(7) (a) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573. (b) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316. (c) Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 9011. (d) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310.
(8) Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1859.

S0022-3263(96)00912-7 CCC: $12.00

Scheme 3

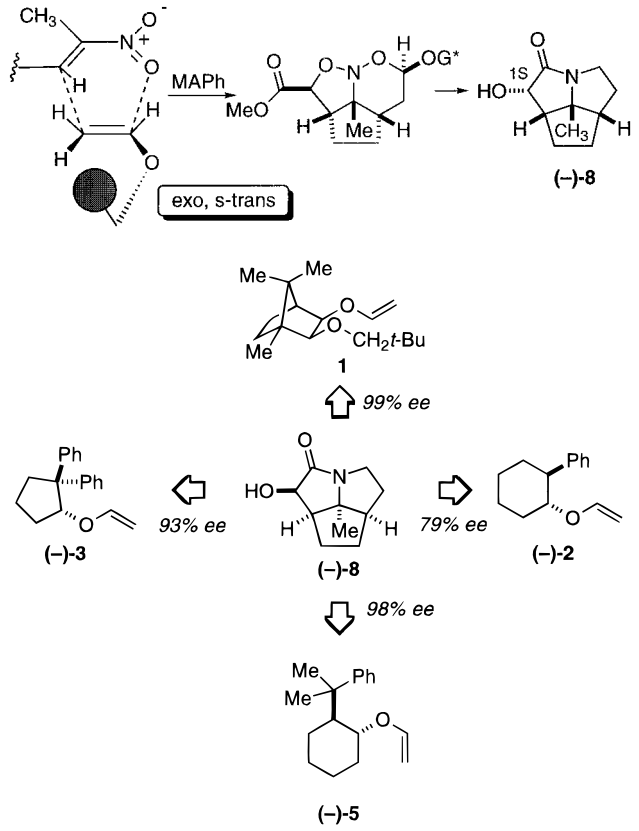


Figure 2. Comparison of auxiliaries used in MAPh promoted cycloadditions (the enantiomer (−)-**5** is depicted for consistency).

88% recovery of (+)-**4**), was levorotatory ($[\alpha]^{25}_D$ −35.6 (CH_2Cl_2, c = 1.15)) and, therefore, belonged to the 1*S* configurational series.[5] To determine the enantiomeric enrichment, (−)-**8** was converted to the 3,5-dinitrophenyl carbamate **9**, which was shown to be highly enantiomerically enriched (98.0% ee) by chiral HPLC.[9]

These results allow formulation of the transition state geometry in the [4 + 2] cycloaddition. To obtain the 1*S* configuration of the α-hydroxy lactam, the vinyl ether must approach the *re*-face of the nitroalkene, Scheme 3.[10] Furthermore, assuming that MAPh is promoting an exo-selective cycloaddition, the vinyl ether must be reacting through an exo-oriented, *s-trans* conformation where the aryl moiety shields the *si*-face of the vinyl ether.

The vinyl ether derived from TCC is a very useful addition to the arsenal of vinyl ethers employed in tandem [4 + 2]/[3 + 2] cycloadditions. The selectivity obtained with (+)-**5** in MAPh-promoted cycloaddition is equal to that of vinyl ether **1**, Figure 2. At the same time this new auxiliary does not suffer from a lengthy and difficult preparation as in the case of **1**. Furthermore, since both enantiomers of TCC are readily available this new auxiliary complements the use of **1** and (−)-**2** for asymmetric nitroalkene cycloaddition reactions in synthesis. The use of (−)-**5** in total synthesis projects highlighting the tandem [4 + 2]/[3 + 2] cycloaddition will be reported in due course.

(9) (a) Pirkle, W. H.; Mahler, G.; Hyun, M. H. *J. Liq. Chromatogr.* **1986**, *9*, 443. (b) Pirkle, W. H.; Pochapsky, T. C.; Burke, J. A.; Deming, K. C. In *Chiral Separations*; Stevenson, D., Wilson, I. D., Eds.; Plenum: New York, 1988; p 23.

(10) The *re* and *si* faces of the diene are defined with respect to nitrogen.

Experimental Section

General Experimental Procedures. See ref 6.

(1*R*, 2*S*)-*trans*-[[2-(1-Methyl-1-phenylethyl)cyclohexyl]-oxy]ethene ((−)-(5)). (−)-**4** (4.00 g, 18.3 mmol, 1.0 equiv) was dissolved in *n*-butyl vinyl ether (260 mL), and $Hg(OAc)_2$ (3.50 g, 11.0 mmol, 0.6 equiv) was added. The solution was heated to reflux for 12 h. An additional portion of $Hg(OAc)_2$ (3.50 g, 11.0 mmol, 0.6 equiv) was added, and the solution was heated to reflux for an additional 12 h. The reaction mixture was allowed to cool to approximately 40 °C, and the mixture was diluted with (500 mL) MTBE and washed with saturated aqueous Na_2CO_3 (3 × 150 mL), and brine (1 × 150 mL). The aqueous layers were back-extracted with CH_2Cl_2 (1 × 500 mL). The combined organic layers were dried (K_2CO_3) and concentrated in vacuo. The crude product was purified by column chromatography on basic alumina activity II (pentane/MTBE (1/0, 1/1/ 0/1)) and distillation to afford 2.77 g (62%) of vinyl ether (−)-**5** and 1.34 g (33%) of recovered alcohol (−)-**4**. For (−)-**5**: ^{1}H NMR ($CDCl_3$) 7.31−7.25 (m, 4H), 7.17−7.13 (m, 1H), 6.15 (dd, *J* = 6.6, 14.2 Hz, 1H), 4.16 (dd, *J* = 1.2, 14.2 Hz, 1H), 3.94 (dd, *J* = 1.4, 6.6 Hz, 1H), 3.54 (dt, J_d = 4.2, J_t = 10.2 Hz, 1H), 2.05−2.08 (m, 1H), 1.88−1.82 (m, 1H), 1.69−1.65 (m, 1H), 1.57−1.53 (m, 1H), 1.44−1.40 (m, 1H), 1.39 (s, 3H), 1.31 (s, 3H), 1.29−1.22 (m 1H), 1.18−1.09 (m, 2H), 0.91−0.81 (m, 1H); ^{13}C NMR ($CDCl_3$) 150.53, 150.15, 127.68, 125.86, 125.02, 87.65, 81.10, 51.92, 40.51, 32.89, 29.00, 27.43, 25.92, 24.94, 24.67; IR (neat) 1630 (m), 1601 (w), 1496 (w); MS (FAB) 245 (M^+ + H, 3), 244 (M^+, 9); $[\alpha]^{25}_D$ −27.9 (CH_2Cl_2, *c* = 1.78); TLC R_f = 0.13 (hexane). Anal. Calcd for $C_{17}H_{24}O$ (244.37): C 83.55; H, 9.89. Found: C, 83.81; H, 9.90.

(2*S*,2a*S*,4a*S*,6*R*,7a*R*,7b*R*)-6-[[(1*S*,2*R*)-*trans*-2-(1-Methyl-1-phenylethyl)cyclohexyl]oxy]octahydro-7b-methyl-1,7-dioxa-7a-azacyclopent[*cd*]indene-2-carboxylic Acid Methyl Ester ((−)-(7)). To a solution of 2,6-diphenylphenol (3.33 g, 13.55 mmol, 6.0 equiv) in CH_2Cl_2 (18 mL) was added trimethylaluminum (2.0 M in toluene, 2.3 mL, 4.51 mmol, 3.0 equiv). Gas evolution was observed, and the resulting light yellow solution was stirred at rt for 30 min.

The Lewis acid was cooled to −65 °C (internal temperature). A solution of vinyl ether ((+)-**5**) (1.10 g, 4.51 mmol, 3.0 equiv) in CH_2Cl_2 (2.6 mL) was added followed by a dropwise addition of **6** (0.300 g, 1.50 mmol, 1.0 equiv) in CH_2Cl_2 (2.6 mL) at a rate keeping the internal temperature below −63 °C. The brown solution was stirred for additional 55 min and then was quenched with MeOH (5.6 mL), poured into CH_2Cl_2 (300 mL), and washed with water (2 × 100 mL) and brine (1 × 100 mL). The aqueous phases were back-extracted with CH_2Cl_2 (2 × 100 mL), the combined organic extracts were dried (Na_2SO_4) and filtered through Celite. The resulting solution was stored at rt for 12 h to ensure complete [3 + 2] cycloaddition and then concentrated in vacuo. The crude product was purified by silica gel column chromatography, eluting with hexane/EtOAc (1/0, 8/1, 6/1, 4/1, 2/1, 1/1). The first fractions contained 2,6-diphenylphenol, which was recrystallized from hexane (80 mL) to afford 2.83 g (85%) of recovered phenol. The second fraction afforded 0.570 g (85%) of a white foam the composition of which was estimated by ^{1}H NMR to be a 1/1.8/145 (endo/exo/exo) mixture of diastereomers (−)-**7**. For (−)-**7**: mp 48−51 °C (hexane/EtOAc); ^{1}H NMR ($CDCl_3$) 7.30−7.24 (m, 4H), 7.14−7.10 (m, 1H), 4.84−4.78 (m, 2H), 3.76 (s, 3H), 3.37(dt, J_d = 4.2 Hz, J_t = 10.2 Hz, 1H), 2.68−2.65 (m, 1H), 2.44−2.40 (m, 1H), 1.95−1.73 (m, 7H), 1.69−1.62 (m, 1H), 1.55−1.51 (m, 1H), 1.48−1.39 (m, 3H), 1.34 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H), 1.21−0.87 (m, 3H); ^{13}C NMR ($CDCl_3$) 170.35, 151.51, 127.72, 125.54, 124.85, 100.05, 87.20, 85.20, 81.67, 56.92, 52.33, 52.17, 43.02, 40.41, 35.36, 31.60, 28.76, 28.49, 27.76, 26.85, 26.52, 26.12, 25.08, 23.67; IR (KBr) 1757 (s), 1741 (m); MS (FAB) 444 (M^+ + H, 3); $[\alpha]^{25}_D$ −25.5 (CH_2Cl_2, *c* = 1.16); TLC R_f = 0.58 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{26}H_{37}NO_5$ (443.58): C, 70.40; H, 8.40; N, 3.15. Found: C, 70.35; H, 8.35; N, 3.12.

(1*S*,3*R*,5a*S*,7a*S*,7b*R*)-Octahydro-1-hydroxy-7b-methyl-2*H*-cyclopenta[*gh*]pyrrolizin-2-one ((−)-8). To a solution of nitroso acetal (−)-**7** (490 mg, 1.10 mmol) in methanol (80 mL) was added a catalytic amount of Raney nickel (W-2). The suspension was stirred for 24.5 h under 1 atm of hydrogen pressure at rt and then was filtered through Celite. The catalyst was washed with MeOH (100 mL), and the combined washes

were filtered through Celite and then concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc (1/1, 1/2, 0/1)) to afford 152 mg (76%) of α-hydroxy lactam (−)-**8** as a white solid along with 213 mg (88%) of recovered alcohol (+)-**5**. For (−)-**8**: mp 91−101 °C (hexane/EtOAc); ^{1}H NMR ($CDCl_3$) 4.69 (dd, J = 2.0, 7.1 Hz, 1H), 3.87 (ddd, J = 3.7, 8.4, 11.8 Hz, 1H), 3.74 (d, J = 3.3 Hz, 1H), 2.90 (ddt, J_d = 1.1, 11.8 Hz, J_t = 7.9 Hz, 1H), 2.60 (q, J = 7.5 Hz, 1H), 2.26−2.21 (m, 1H), 2.15−2.05 (m, 1H), 1.78−1.68 (m, 3H), 1.51−1.42 (m, 1H), 1.28 (s, 3H), 1.27−1.19 (m, 1H); ^{13}C NMR ($CDCl_3$) 176.44, 75.63, 72.82, 51.10, 49.19, 42.10, 31.45, 31.00, 24.80, 22.86; IR (KBr) 1694 (s), 1464 (w); $[\alpha]^{25}_D$ −35.6 (CH_2Cl_2, c = 1.15).

(1*S*,3*R*,5a*S*,7a*S*,7b*R*)-1-[*N*-(3,5-Dinitrophenyl)carbamoxy]-7b-methyloctahydro-2*H*-cyclopenta[*gh*]pyrrolizin-2-one (9). A solution of 3,5-dinitrobenzoyl azide (58 mg, 0.24 mmol, 1.1 equiv) in toluene (10.0 mL) was heated to reflux for 5 min, and then a solution of α-hydroxy lactam (−)-**8** (40 mg, 0.22 mmol, 1.0 equiv) in toluene (2.0 mL) was added. The solution was heated to reflux for 95 min and then was allowed to cool to rt. The reaction mixture was concentrated in vacuo, and the crude product was purified by column chromatography (hexane/EtOAc (4/1, 2/1, 1/1, 1/2, 0/1)) to afford 76 mg (88%) of **9** as a slightly yellow solid. For **9**: ^{1}H NMR ($CDCl_3$) 10.50 (s, 1H, NH), 8.58 (s, 1H), 8.52 (s, 2H), 5.96 (d, J = 7.2 Hz, 1H), 3.93 (ddd, J = 3.6, 8.4, 12.0 Hz, 1H), 3.08 (dt, J_d = 11.9 Hz, J_t = 7.8 Hz, 1H), 2.80 (q, J = 7.2 Hz, 1H), 2.39−2.37 (m, 1H), 2.28−2.21 (m, 1H), 1.91−1.79 (m, 2H), 1.74−1.66 (m, 1H), 1.55−1.47 (m, 1H), 1.44 (s, 3H), 1.41−1.23 (m, 1H); ^{13}C NMR ($CDCl_3$) 172.20, 152.49, 148.52, 141.21, 118.00, 112.31, 76.10, 74.69, 49.41, 42.37, 31.61, 30.95, 25.77, 22.61; IR (KBr) 1744 (m), 1686 (s); HPLC (Pirkle covalent L-naphthylalanine (250 × 4.5 mm, 5 m (Regis)), (hexane/EtOAc, 7/3, 1.5 mL/min)) t_R (1*R*,3*S*,5a*R*,7a*R*,7b*S*)-**9**, 6.6 min (0.98%); t_R (1*S*,3*R*,5a*S*,7a*S*,7b*R*)-**9**, 18.4 min (99.01%).

Acknowledgment. We are grateful to the National Institutes of Health (GM-30938) for financial support. A.T. thanks the University of Illinois for a Graduate Fellowship.

JO960912C