Asymmetric Cyclopentannelation. Axial to Tetrahedral Chirality Transfer

Huaping Hu, David Smith,[1] Roger E. Cramer,[1] and Marcus A. Tius*

Department of Chemistry, 2545 The Mall University of Hawaii, Honolulu, Hawaii 96822

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We recently applied a variant of the Nazarov reaction[2] to the preparation of cross-conjugated prostaglandins.[3] During this work we observed a pronounced preference (ca. 6/1) for formation of the Z isomer of the exocyclic double bond (**3**, Scheme 1) during

Scheme 1
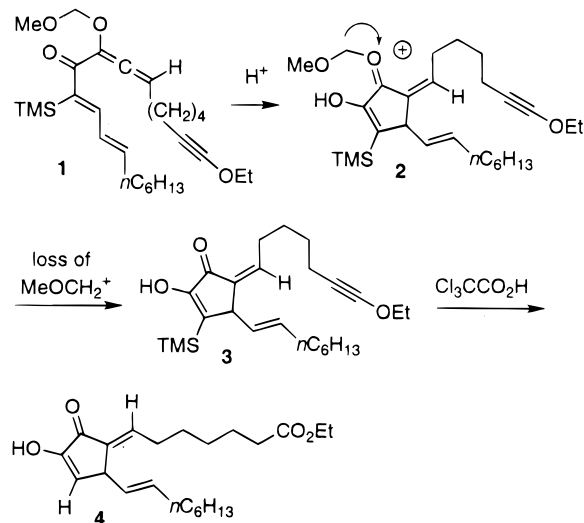
the cyclization step. Allenyl ketone **1**, which was not isolated, underwent cyclization spontaneously during workup with aqueous sodium dihydrogen phosphate. Loss of the methoxymethyl carbocation from the presumed intermediate **2** leads to the observed product. Exposure of **3** to moist trichloroacetic acid at room temperature led to complete equilibration of the exocyclic double bond to the thermodynamically favored E geometry.[4]

We had postulated that the preference for the Z geometry was due to a steric bias in favor of one of the two possible modes for conrotatory ring closure of **1**. This implied that in the case of chiral allenes, control of the sense of conrotation would have the effect of transferring the axial chirality of the allene to the tetrahedral ring carbon (C4 in **6E** and **6Z**; Figure 1) provided
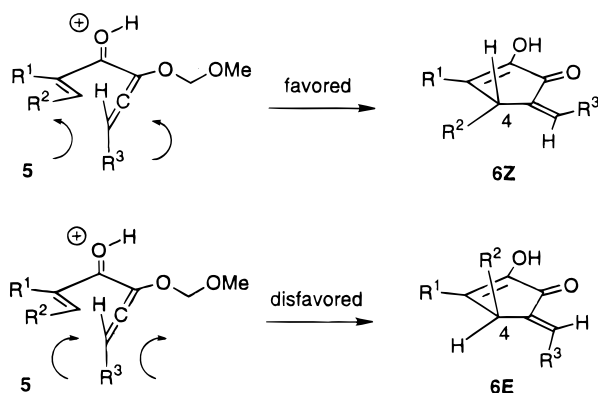
Figure 1.

Wagner−Meerwein rearrangements of the intermediates do not take place,[5] and that other nonconcerted pathways do not compete with the concerted conrotation. As a corollary, transfer of asymmetry should take place more efficiently when R^3 is large, other factors being equal. In this Communication we present our findings which support this hypothesis.

The first task was to prepare a nonracemic allene. Although syntheses of chiral, nonracemic allenes are known,[6] none are suitable for the preparation of allenyl methoxymethyl ethers. Consequently, resolution of the enantiomers was accomplished by chiral HPLC (Scheme 2).[7] In a separate series of experiments, methoxymethyl propargyl ethers **7a** and **7b** were isomerized to allenes **8a** and **8b**.[2a] α-Deprotonation followed by trapping with CO_2 led to acids **9**, which were converted to morpholino amides **10**.[8] Resolution by chiral HPLC (Chiralcel OD, 10 mm × 250 mm) produced the more mobile dextrorotatory and the less mobile levorotatory enantiomers. Exposure of (−)-**10a** (93% ee) to vinyllithium species **11**,[9] followed by aqueous workup, led to Z-cyclopentenone (+)-**12a** (78% ee, 84% chirality transfer) as the major product (50% yield), along with 9% of E-cyclopentenone (−)-**13a** (64% ee). The minor isomer (−)-**13a** is formed primarily from the disfavored conrotation rather than from Z to E isomerization of **12a**. This was shown by converting (+)-**12a** to (+)-**14a**[10] and (−)-**13a** to the enantiomer (−)-**14a**. The lower ee of (−)-**13a** indicates that some Z to E isomerization had taken place, possibly during workup. These results demonstrated that axial to tetrahedral transfer of chirality had taken place,[11] but provided no information for the direction in which this had occurred. Support for the mechanism of Figure 1 requires knowledge of the absolute stereostructures of starting material and product. The problem was solved as follows. Combination of (+)-**10b** (98% ee) with **11** led to the Z isomer (−)-**12b** (95% ee, >95% chirality transfer) in 64% yield (Scheme 3). None of

(1) Authors to whom inquiries should be directed concerning the X-ray crystallographic analysis.

(2) (a) Tius, M. A.; Hu, H.; Kawakami, J. K.; Busch-Petersen, J. *J. Org. Chem.* **1998**, *63*, 5971−5976. (b) Tius, M. A.; Drake, D. J. *Tetrahedron* **1996**, *52*, 14651−14660. (c) Tius, M. A.; Kwok, C.-K.; Gu, X.-q.; Zhao, C. *Synth. Commun.* **1994**, *24*, 871−885. (d) Tius, M. A.; Zhou, X.-m. *Tetrahedron Lett.* **1989**, *30*, 4629−4632. (e) Tius, M. A.; Astrab, D. P. *Tetrahedron Lett.* **1989**, *30*, 2333−2336. (f) Tius, M. A.; Trehan, S. *J. Org. Chem.* **1989**, *54*, 46−51. (g) Tius, M. A.; Astrab, D. P.; Fauq, A. H.; Ousset, J.-B.; Trehan, S. *J. Am. Chem. Soc.* **1986**, *108*, 3438−3442. For related work involving Nazarov cyclizations of allenyl ketones see: Hashmi, A. S. K.; Bats, J. W.; Choi, J.-H.; Schwarz, L. *Tetrahedron Lett.* **1998**, *39*, 7491−7494. For related work, see: Jacobi, P. A.; Armacost, L. M.; Kravitz, J. I.; Martinelli, M. J.; Selnick, H. G. *Tetrahedron Lett.* **1988**, *29*, 6865, et seq.

(3) Tius, M. A.; Busch-Petersen, J.; Yamashita, M. *Tetrahedron Lett.* **1998**, *39*, 4219−4222.

(4) Had the cyclization of **1** to **3** not taken place spontaneously under mild conditions, the kinetic preference for the formation of **3** would not have been detected, since isomerization would have certainly been rapid under the conditions of a conventional acid-catalyzed Nazarov reaction.

(5) Morel-Fourrier, C.; Dulcere, J.-P.; Santelli, M. *J. Am. Chem. Soc.* **1991**, *113*, 8062−8069. Motoyoshiya, J.; Yazaki, T.; Hayashi, S. *J. Org. Chem.* **1991**, *56*, 735−740.

(6) For leading references, see: Mikami, K.; Yoshida, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 858−860. See also: Noguchi, Y.; Takiyama, H.; Katsuki, T. *Synlett* **1998**, 543−545. Alexakis, A.; Mangeney, P.; Ghribi, A.; Marek, I.; Sedrani, R.; Guir, C.; Normant, J. F. *Pure Appl. Chem.* **1983**, *60*, 49−56.

(7) Krause, N.; Handke, G. *Tetrahedron Lett.* **1991**, *32*, 7225−7228.

(8) Einhorn, J.; Einhorn, C.; Luche, J.-L. *Synth. Commun.* **1990**, *20*, 1105−1112.

(9) Vinyllithium **11** was generated by metal−halogen exchange from the iodide. See: Chen, S.-H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834−5845. Le Noble, W. J. *J. Am. Chem. Soc.* **1961**, *83*, 3897−3899. Terrel, L. R.; Ward, J. S., III; Maleczka, R. E., Jr. *Tetrahedron Lett.* **1999**, *40*, 3097−3100.

(10) Gilbert, A. In *Photochemistry in Organic Synthesis*; Coyle, J. D., Ed.; Burlington House: London, 1986; p 141.
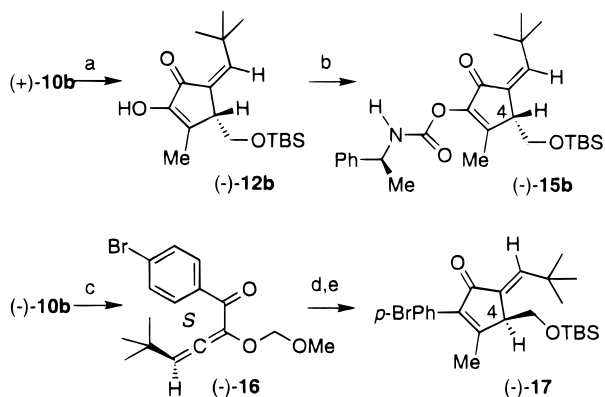
(11) For a recent example, see: Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348−5349.

Scheme 2
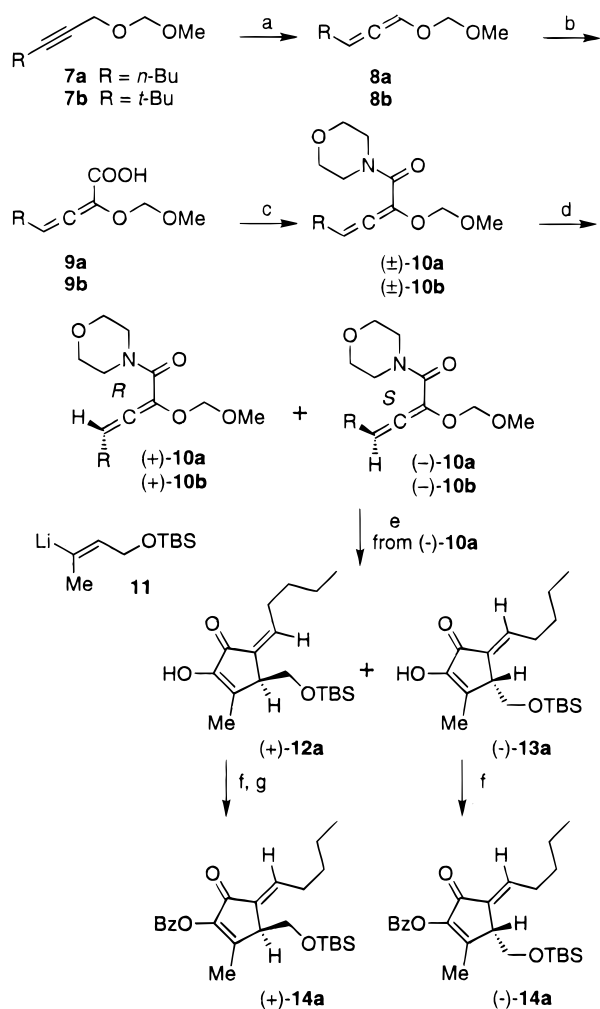
^{a} *n*-BuLi, THF, −78 °C, 2 h; **8a** 64%, **8b** 88%. ^{b}*n*-BuLi, THF, −78 °C, 30 min; CO$_2$(s). ^{c}Et$_3$N, PPh$_3$, CBr$_4$, morpholine, CH$_2$Cl$_2$, 0 °C; (±)-**10a** 68% from **8a**, (±)-**10b** 76% from **8b**. ^{d}Chiralcel OD, 20% ^{i}PrOH in hexanes. ^{e}Add to **11**, THF, −78 °C, 30 min; **12a** 50%, **13a** 9%. ^{f}Et$_3$N, CH$_2$Cl$_2$, PhCOCl. ^{g}Sunshine, PhH; (+)-**14a** 80%, (−)-**14a** 95%.

Scheme 3

^{a} **11**, THF, −78 °C, 30 min, 64%. ^{b}Et$_3$N, CH$_2$Cl$_2$, (*S*)-α-methylbenzyl isocyanate, 0 °C, >90%. ^{c}*p*-Bromophenyllithium, THF, −78 °C, 30 min, 72%. ^{d}**11**, THF, −78 °C, 30 min, 69%. ^{e}CH$_2$Cl$_2$, BF$_3$·Et$_2$O, −78 °C, 57%.

the *E* isomer was detected in the reaction product. The absence of the byproduct as well as the greater optical purity of **12b** compared to **12a** lend support to the postulated mechanism. Conversion of the free hydroxyl group in **12b** to the carbamate with (*S*)-α-methylbenzyl isocyanate led to crystalline (−)-**15b**.

X-ray crystallography elucidated the relative stereochemistry in **15b**.[12] From the known absolute configuration, (*S*), of the isocyanate, the absolute stereochemistry at C4 in (−)-**12b** was determined to be (*R*).

To determine the absolute stereochemistry of the allene, levorotatory morpholino amide (−)-**10b** was combined with *p*-bromophenyllithium to give crystalline phenone (−)-**16** (Scheme 3). The absolute stereochemistry of (−)-**16** was determined crystallographically to be (*S*), as shown.[13] Therefore (−)-**10b** is also (*S*), (+)-**10b** is (*R*), and the cyclization which produced **12b** occurred via one of the two 4π conrotations, as shown in Figure 1 (see **5**: R^1 = CH$_3$, R^2 = CH$_2$OTBS, R^3 = *t*-Bu). Although we were not able to prepare crystalline derivatives from any of the materials derived from **10a**, the absolute stereostructures of **12a**, **13a**, and **14a** can reasonably be inferred from these results and from the optical rotations.

Exposure of (−)-**16** to **11** led to a diastereomeric mixture (ca. 2:1) of tertiary alcohols. Cyclization and *Z* to *E* isomerization in situ to (−)-**17** took place in 57% yield under the influence of BF$_3$·Et$_2$O. Chirality transfer in this case was >90%, which indicates that both tertiary alcohols led to the same intermediate cation. This result shows that the effect is likely to be quite general.

Highly efficient chirality transfer from an allene to tetrahedral carbon has been realized during the course of a modified Nazarov cyclization. The stereochemical outcome can be predicted according to a conrotation in which the distal group on the allene rotates away from the alkene (Figure 1). The difference in the level of chirality transfer between **10a** and **10b** suggests a steric origin for the torquoselectivity of the process.[14] The utility of the cyclization has already been demonstrated in our group in the context of the synthesis of racemic cyclopentanoid natural products.[2b,e,f,3,15] Work is in progress to develop convenient methods for asymmetric synthesis of allenyl ethers so as to realize the full potential of the methodology.[16]

Supporting Information Available: Experimental details for the preparation of (−)-**12b**, (−)-**15b**, and (−)-**16**, ^{1}H, ^{13}C NMR, IR of (+)-**10b**, (−)-**12b**, (−)-**15b**, (−)-**16**, and mass spectra for (+)-**10b** and (−)-**12b**; tables listing full crystallographic information, atomic coordinates, thermal parameters, and bond distances and angles for (−)-**15b** and (−)-**16**; and ORTEP diagrams for (−)-**15b** and (−)-**16** (PDF). This material is available free of charge via the Internet at htpp://pubs.acs.org.

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(12) (−)-**15b**: dimensions 0.13 × 0.13 × 1.0 mm, orthorhombic, *P*2$_1$2$_1$2, *a* = 15.65(2) Å, *b* = 29.43(4) Å, *c* = 6.833(8) Å, *V* = 3147(7) Å^3, *z* = 4, Nicolet P3 using graphite monochromated Mo Kα radiation. A total of 2652 reflections were measured, and 1862 unique (2θ < 35°, *r*$_{int}$ = 0.1284) reflections were used in refinement. Solved by direct methods and refined by full-matrix least squares on *F*^{2} that converged to *R*$_1$ = 0.0713 (*I* > 2σ), *R*$_1$ = 0.1257 (all data), *wR*^{2} = 0.1740 (*I* > 2σ), *wR*^{2} = 0.1989 (all data), absolute structure parameter 0.4(8).

(13) (−)-**16**: dimensions 0.2 × 0.2 × 1.0 mm, monoclinic, *P*2$_1$, *a* = 11.40-(2) Å, *b* = 6.61(1) Å, *c* = 11.41(2) Å, β = 97.07(1)°, *V* = 853(3) Å^3, *z* = 2, Nicolet P3 using graphite monochromated Mo Kα radiation. A total of 2605 reflections were measured, and 1210 unique (2θ < 45°, *r*$_{int}$ = 0.1561) reflections were used in refinement. Solved by Patterson methods and refined by full-matrix least squares on *F*^{2} that converged to *R*$_1$ = 0.0800 (*I* > 2σ), *R*$_1$ = 0.1860 (all data), *wR*^{2} = 0.1769 (*I* > 2σ), *wR*^{2} = 0.2196 (all data), absolute structure parameter −0.01(5).

(14) Denmark, S. E.; Wallace, M. A.; Walker, C. B., Jr. *J. Org. Chem.* **1990**, *55*, 5543−5545. For an illumination review, see: Dolbier, W. R., Jr.; Koroniak, H.; Houk, K. N.; Shen, C. *Acc. Chem. Res.* **1996**, *29*, 471.

(15) Harrington, P. E.; Tius, M. A. *Org. Lett.* **1999**, *1*, 649−651.

(16) The referees correctly pointed out that the practical significance of the method which is described in this manuscript is limited by the lack of practical means for the enantioselective preparation of allenyl ethers. A solution to this problem was developed in our group after the submission of this manuscript: Harrington, P. E.; Tius, M. A. Unpublished.