synthesis of alkaloids is under investigation.

Acknowledgment. This research was supported by grants from the National Institutes of Health (GM-07874 and GM-31350). A PHS postdoctoral fellowship to R. Frechette is gratefully acknowledged. We also thank Ms. Jan Cook for providing valuable assistance with the desilylation reactions.

Supplementary Material Available: Spectroscopic data for all new compounds (6 pages). Ordering information is given on any current masthead page.

Stereoselective Synthesis of Exocyclic Alkenes via Zirconium-Promoted Alkyl–Diene Coupling[1]

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Received September 5, 1989

Summary: The reaction of 1-vinyl-1-cycloalkenes with 1 equiv of $(RCH_2CH_2)_2ZrCp_2$, where R is H or alkyl, followed by treatment with electrophiles, e.g., proton donors, I_2, and ketones, can provide the corresponding exocyclic alkenes in good yields, the stereoselectivity being ≥95%.

Sir: We have recently reported the reactions of "$ZrCp_2$", such as *n*-Bu_2ZrCp_2,[2,3] with nonconjugated enynes,[3,4] diynes,[2,3,5] and dienes.[1] With *n*-Bu_2ZrCp_2 the actual "$ZrCp_2$" reagent has been shown to be (η^2-1-butene)$ZrCp_2$ (**1a**), in which 1-butene serves as a $ZrCp_2$-protecting but "nonparticipating" ligand.[3,6] On the other hand, the reaction of alkene–$ZrCp_2$ complexes (1) with monoalkenes incorporates the alkene moiety in the products.[7]

$(RCH_2CH_2)_2ZrCp_2 \longrightarrow$

a: R = Et. b: R = H.

(1)

We now report that the reaction of 1 with conjugated dienes (**2**) gives zirconacycles represented by **3**, which can be converted to a variety of organic products, such as **4–6** shown in Scheme I. Particularly noteworthy is that 1-vinyl-1-cycloalkenes can be readily converted to stereodefined exocyclic alkenes.[8,9] Although zirconacycles represented by **3** have been previously prepared by the reaction of alkenes with conjugated diene–$ZrCp_2$ complexes obtained by either the enediylmagnesium–Cl_2ZrCp_2 reaction[10a] or the diene–Ar_2ZrCp_2 reaction,[10b] the conversion of **2** to **3** as shown in Scheme I represents a novel route. Furthermore, the conversion of 1-vinyl-1-cycloalkenes to stereodefined exocyclic alkenes has not been previously reported.

Table I. Synthesis of Exocyclic Alkenes by the Reaction of Conjugated Dienes with Dialkylzirconocenes

conjugated diene	R of R_2ZrCp_2	exocyclic alkene	yield, % GLC	yield, % isolated
2a	Et	**4a**	91	56
2a	Et	**7**	–	55
2a	Et	**8**	–	66
2a	Et	**5a**	55	48
2a	*n*-Bu	**4b**	90	80
2b	Et	**4c**	82	67
2b	*n*-Bu	**4d**	89	72
2c	Et	**4e**	67	64
2c	*n*-Bu	**4f**	–	70
2d	*n*-Bu	**4g**	83	68

Typically, ethyllithium in Et_2O (1.0 M, 6.0 mL, 6.0 mmol) was added to a solution of Cp_2ZrCl_2 (0.88 g, 3.0 mmol) in 10 mL of THF at −78 °C. After having been stirred for 1 h at −78 °C, the mixture was treated with 1-ethenyl-1-cyclohexene (0.325 g, 3.0 mmol), and warmed to 25 °C over a few hours. Examination of the reaction mixture by ^1H NMR spectroscopy using benzene as an internal standard indicated the formation of a $ZrCp_2$ derivative exhibiting two singlets for the Cp groups at δ 5.50 and 5.65 in >90% yield. The compound has been tentatively identified as **3a** on the basis of the following. The reaction mixture obtained above was quenched with a mixture of 2 N HCl and Et_2O, extracted with Et_2O, washed with aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Distillative workup gave 0.23 g (56%) of butylidenecyclohexane: IR (neat) 3030 (w), 1675 (w), 1450 (s), 1370 (m) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.88 (t, J = 7 Hz, 3 H), 1.25–1.4 (m, 2 H), 1.4–1.7 (m, 6 H), 1.9–2.0 (m, 2 H), 2.0–2.2 (m, 4 H), 5.07 (t, J = 7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.75, 27.89, 28.11, 28.17, 28.77, 29.18, 37.24, 121.27, 139.56. Treatment of **3a** with D_2O (1 mL/3 mmol of diene, 25 °C, 2 H) followed by workup with 2 N HCl produced a >95% pure monodeuterio derivative of **4a**, i.e., **7**, in 55% isolated yield. The use of 2 N DCl in place of HCl cleanly produced the dideuterio derivative **8** in 66% yield, the extents of deuterium incorporation on the ring

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(7) Swanson, D. R.; Rousset, C. J.; Negishi, E.; Takahashi, T.; Seki, T.; Saburi, M.; Uchida, Y. *J. Org. Chem.* **1989**, *54*, 3521.
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Scheme I

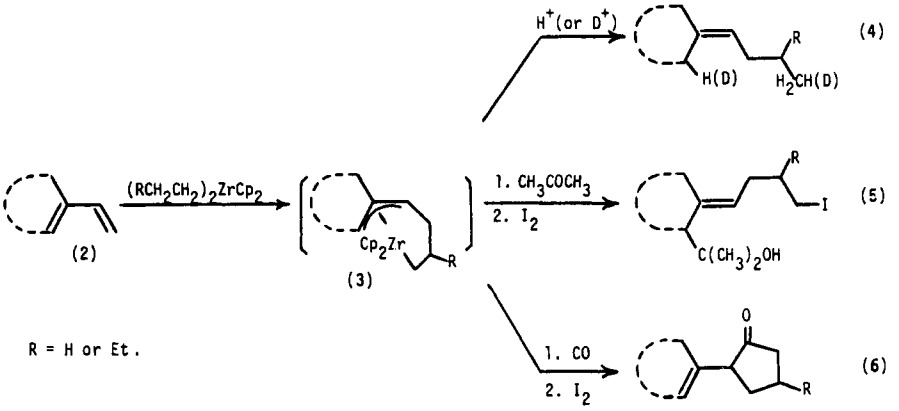
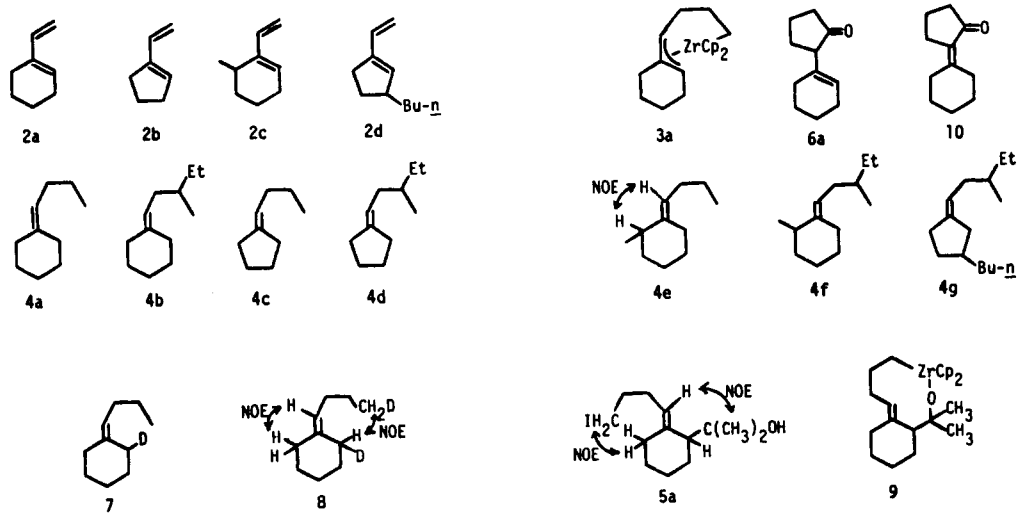
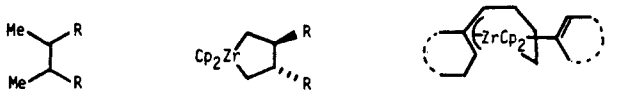


Chart I



and the chain terminus were both ≥95%. Interestingly, treatment of **3a** first with dry acetone and then with I_2 provided a 55% yield of **5a**, in which the sense of alkene geometry is opposite to that in **4a**. The stereochemistry of **5a** corresponds to the probable intermediacy of **9**. The reaction of **3a** with CO (1.1 atm) at 0 °C for 2 h followed by iodinolysis (1.1 equiv) gave a 47% yield of **6a** and its regioisomer **10** in a 90:10 ratio (see Chart I).

The results of the conversion of conjugated dienes into exocyclic alkenes **4a–g** as well s **5a**, **7**, and **8** are summarized in Table I. The most noteworthy feature is that all of the exocyclic alkene products are ≥95% isomerically pure single isomers, as judged by analysis of ^1H and ^{13}C NMR spectra as well as GLC. The results indicate that the reaction is not only ≥95% regioselective but also ≥95% stereoselective in cases where the exocyclic alkenes are stereodefined, as in the cases of **4e–g**, **5a**, **7**, and **8**. The stereochemical assignment is based on ^1H 2D NOESY NMR analysis of selected products, i.e., **4e**, **5a**, and **8**. Highly intriguing is that even **4f** and **4g** exhibit only one set each of ^{13}C NMR signals. Although the relative stereochemical relationship between two asymmetric carbon centers has not been established, these compounds must be single diastereomers. The required regiodefined dienes were prepared by the Pd-catalyzed reaction of vinylzinc chloride[11a] with the corresponding cycloalkenyl triflates.[11b] That the conversion of conjugated dienes into alkylated alkenes is not limited to cyclic derivatives is indicated by the preparation of 2,5-dimethyl-2-heptene in 83% GLC yield (53% isolated) via the *n*-Bu_2ZrCp_2–isoprene reaction. The "pair" selectivity of the reaction is also ≥95%. Only traces of the homocoupled products, i.e., **11**, and dimers of **2** were formed. The observed high "pair" selectivity is readily explained on the assumptions that **4**, which must be allylically stabilized, is more stable than **12** and that the 1:1 reactant ratio would dictate the amount of the other possible pair, i.e., **13**, to be the same as that of **12**. The high "pair" selectivity is reminiscent of the *n*-Bu_2ZrCp_2–styrene reaction reported recently by us,[7] in which benzylic stabilization is thought to play a similar role.



11 (R = H or Et) 12 (R = H or Et) 13

Only in the reaction of **14** were some abnormal results observed. Thus, its reaction with *n*-Bu_2ZrCp_2 at −78 to 0 °C followed by protonolysis produced **15** in 81% GLC yield (46% isolated) which was isomerically ≥95% pure. Even more puzzling is that the cyclization reaction followed by carbonylation produced isomerically ≥95% pure **16** as essentially the only bicyclic carbonylation product, albeit only in 27% isolated yield. Its identification is primarily based on ^1H and ^{13}C NMR analysis including extensive decoupling and 2D NOESY experiments. At present, we cannot readily rationalize its formation.

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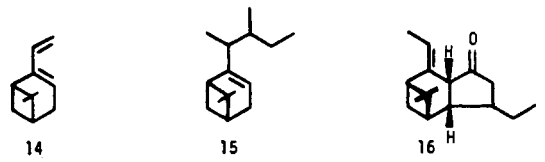

14 15 16

The present study adds to the growing list of highly stereoselective methods for preparing exocyclic alkenes.[9] Finally, we made an erroneous claim that the reaction of 1,3-butadiene with n-Bu_2ZrCp_2 gave (1,3-butadiene)$ZrCp_2$.[2] In the light of the results presented herein, we wish to correct this error with apology.

Acknowledgment. We thank the National Science Foundation (Grant CHE-8842237) and the National Institutes of Health (Grant GM36792) for support. We acknowledge that this study was triggered by an observation in 1987 by Dr. Y. Zhang of our laboratory that the reaction of 1-vinyl-1-cyclohexene with n-Bu_2ZrCp_2 produced an n-Bu-incorporated product **4b**. We also thank Dr. G. Wu for technical assistance in obtaining some NMR spectra.

Total Synthesis of 13-Oxygenated Prostanoids Derived from Arachidonate: An Instance of Extraordinary Variability in the Stereochemical Sense of a Mukaiyama Aldol Reaction

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Received September 18, 1989

Summary: A complete reversal of stereochemical outcome in the Mukaiyama reaction of oct-2-ynal as opposed to either (*E*)- or (*Z*)-oct-2-enal with a common enoxysilane has been noted and applied to a very straightforward synthesis of the titled series.

Sir: The principal 9α,11α-endoperoxides arising from the in vivo oxidation of arachidonate, in the presence of PGH synthase, contain a trans 13,14-double bond and either 15(*S*)-hydroperoxy (PGG_2) or 15(*S*)-hydroxy (PGH_2) functions.[1,2] Surprisingly, it was recently shown that this process also produces isomers of the above, bearing oxygen substitution at C_{13} (Scheme I). Reduction of this endoperoxide gives rise to the allylic isomer of $PGF_{2\alpha}$.[2,3] That this prostaglandin is properly represented by structure 1 was demonstrated by Hofmann and colleagues. The four permutants bearing a 13-hydroxy group and a Δ^{14} double bond were synthesized.[4] A minor synthetic product, shown to be compound 1, corresponded to the naturally derived product.

It was our intention to provide the difficulty accessible compound 1 through total synthesis. Recently we described two concise syntheses of $PGF_{2\alpha}$[5] (Scheme II). Each synthesis involved a stereospecific aldol-like reaction,[6] catalyzed by titanium tetrachloride, between enoxysilane **4**[7] and the α,β-unsaturated aldehydes (*Z*)- and (*E*)-2-octenal. Each aldol reaction occurred with transfer of the triethylsilyl group to afford **5** and **6**, respectively, wherein, in each case, the configuration at C_{13} is *R*.[8] In principle, one could envision one of several protocols to bring about an overall inversion at C_{13} with preservation of the *Z*-Δ^{14} unsaturation for the conversion of compound **4** to **1**. In practice a much simpler route was discovered.

The key reaction was that of enoxysilane **4** with oct-2-ynal (**7**).[9] As in the previous work,[5] the reaction was carried out in methylene chloride in the presence of titanium tetrachloride (1 equiv). There was thus obtained an acetylenic alcohol. Unlike the reactions with the two enals, we could not observe any of the silyl group transfer product. At this stage, it was not possible to determine the stereochemistry at C_{13} in this product. Semihydrogenation of the triple bond (H_2; Lindlar catalyst; 50 min) afforded a *Z*-allylic alcohol, which, upon acetylation (Ac_2O, Py, DMAP), afforded a *Z*-allylic acetate in 50% overall yield from **3**. This compound did not converge with any transformation products of **5**. *Our suspicion that the noncorrespondence arose from a differing configuration at C_{13}[8] was confirmed.* The allylic acetate, thus formulated as **9**, upon treatment with $PdCl_2(MeCN)_2$[10] afforded compound **11**. The same compound was obtained from the allylic transposition carried out in the same way on the 13-acetate derived from **6**.[5] The structure of **11** is secure in that it had been converted to $PGF_{2\alpha}$[5] by a sequence that

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(8) The reader will not be confused at the fact that the *R* and *S* descriptors for compounds **6**, **7**, and **8** (13*R* in each case) fail to communicate the fact that the relative configuration at C_{13} is opposite in **8** from that of **5** and **6**. This situation is better captured by focusing on the C_{12}–C_{13} relationship, which may be said to be syn in **5** and **6** (in the zig-zag conformer shown) and anti in **8**.
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