Articles

Rh-Mediated Cyclopentane Construction Can Compete with β-Hydride Elimination: Synthesis of (±)-Tochuinyl Acetate[1]

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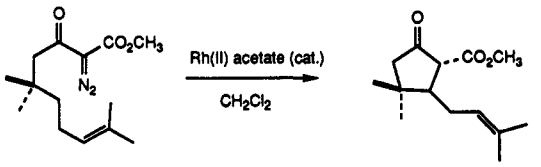
Rhodium(II) carboxylate catalyzed C–H insertion to form a cyclopentane is shown to compete effectively with β-hydride elimination, except when the β hydrogen is ternary. Cyclization of diazo ester **27** gives **28**, which is converted in three steps to (±)-tochuinyl acetate **25**. Both the cyclization to form **28** and the alkylation of **28** proceed with remarkable diastereoselectivity.

Introduction

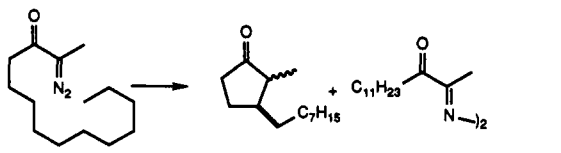
Most methods for carbocyclic ring construction depend on the joining of previously functionalized carbon atoms. We and others[2,3] have found that rhodium(II) carboxylate mediated intramolecular C–H insertion (e.g., **1** → **2**), involving bond formation to a previously *unfunctionalized* carbon atom, is a powerful method for the construction of both carbocycles, especially cyclopentanes, and heterocycles.



1 **2**

To date, there has been no example reported[4] of Rh(II)-catalyzed C–H insertion in which there was also a C–H bond β to the α-diazo ketone (e.g., **3** → **4**). This is not surprising, as it might be expected that the well-known[5] β-hydride elimination would intervene, to give **5**. We now report that under some circumstances the desired cyclopentane formation can in fact compete effectively with elimination.

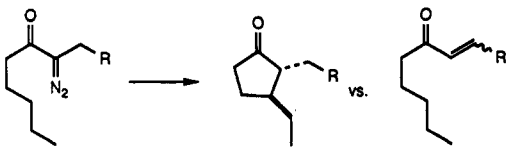
Table I. Rh(II)-Catalyzed Reactions of Diazoethyl Ketone 9



9 **10** **11**

	Rh(II) ligand	yield,[a] %	10, %	11,[b] %
1	CF_3CO_2–	89	77	23
2	CH_3CO_2–	82	77	23
3	*o*-(PhO)$C_6H_4CO_2$–	78	79	21
4	CF_3CO_2–[c]	82	85	15

[a] Yield (10 + 11) of pure chromatographed material. [b] Yield based on 2 mmol of diazo ketone givien 1 mmol of dimer. [c] This reaction was run in Schlenkware under N_2, with methylene blue added.



3 **4** **5**

Relative Reactivity of C–H Bonds. Empirically,[3,6] ternary C–H sites are more reactive for insertion or elimination than secondary C–H sites, which in turn are more reactive than primary C–H sites. A benzylic site is less reactive than an aliphatic site carrying the same substitution.[3a] Electron-withdrawing substituents several atoms away can deactivate a C–H insertion site.[7] Given these considerations, it seemed that β-hydride elimination would be least likely with an α-diazo β-methyl (diazoethyl) ketone. We have confirmed this (see next section) and have found that α-diazo β-methylene ketones and esters can also cyclize efficiently (following sections). The single α-diazo β-methine ester we have tried gave exclusively β-hydride elimination (**6** → **7**), with no trace of cyclopentane **8**.

(1) Presented in part at the 12th Conference on the Catalysis of Organic Reactions, San Antonio, TX, April 1988, and the 5th International Symposium on Carbene Chemistry, Kyoto, Japan, Nov 1989.

(2) (a) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808. (b) For the first examples of cyclopentane constructure by Rh-catalyzed intramolecular C–H insertion, see: Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; da Silva, R. R.; Shulman, S.; Warnet, R. J. *J. Org. Chem.* **1982**, *47*, 3242.

(3) (a) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686. (b) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (c) Taber, D. F. Carbon–carbon bond formation by C-H insertion. In *Comprehensive Organic Synthesis*; Pergamon Press: New York, in press. (d) Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *J. Org. Chem.* **1991**, *56*, 1434.

(4) Two low-yield examples of 1,5-insertion to make heterocycles have been reported: (a) Guzman, A.; Pinedo, A.; Saldana, A.; Torre, D.; Muchowski, J. M. *Can. J. Chem.* **1983**, *61*, 454. (b) Cama, L. D.; Christensen, B. G. *Tetrahedron Lett.* **1978**, 4233. (c) Very recently, Padwa reported Rh-catalyzed preparation of a 1,3-dipole from an α-diazo β-methylene ester without competing β-hydride elimination: Padwa, A.; Kulkarni, Y. S.; Zhang, Z. *J. Org. Chem.* **1990**, *55*, 4144.

(5) (a) Ikota, N.; Takamura, N.; Young, S. D.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 4163. (b) Hudlicky, T.; Olivo, H. F.; Natchus, M. G.; Umpierrez, E. F.; Pandolfi, E.; Volonterio, C. *J. Org. Chem.* **1990**, *55*, 4767. (c) Frazen, V. *Ann.* **1957**, *602*, 199.

(6) McDonald, R. N.; Jones, M. T. *J. Am. Chem. Soc.* **1986**, *108*, 8097.

(7) Stork, G.; Nakatani, K. *Tetrahedron Lett.* **1988**, *29*, 2283.

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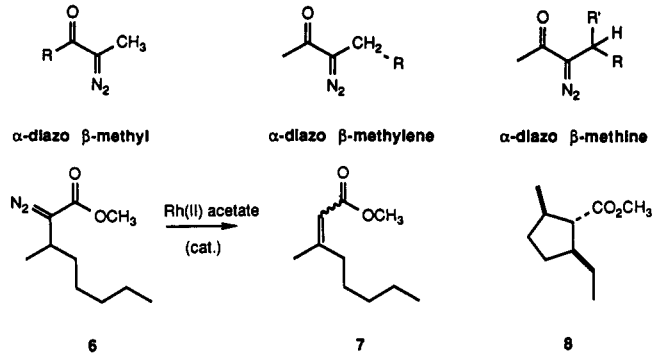


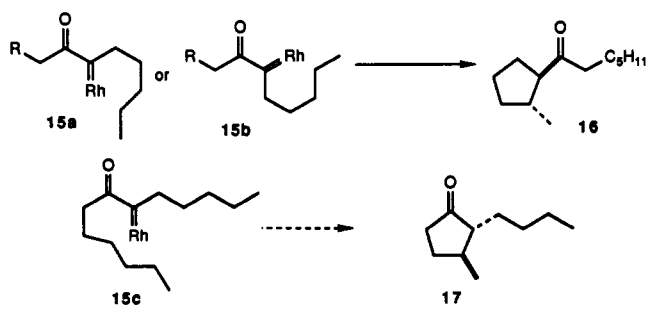
6 7 8

Cyclization of an α-Diazo β-Methyl Ketone. Diazoethyl ketones have been shown by Hudlicky and others[8] to participate efficiently in intramolecular cyclopropanation reactions. We have now found that diazoethyl ketone **9** (Table I), prepared[8] by addition of diazoethane to lauroyl chloride, cyclizes under Rh(II) catalysis to ketone **10**. The major competing side reaction is not β-hydride elimination, to form the vinyl ketone, but rather formation of a dimer **11**. Neither the yield of the cyclization nor the relative proportion of the two products is much affected by changing the ligands on the Rh(II) carboxylate. The maximum yield of the desired cyclopentane (Table I, entry 4) was achieved by minimizing oxygen (freeze–thaw degassing, Schlenkware) and adding a trace of methylene blue to the reaction mixture.

Cyclization of an α-Diazo β-Methylene Ketone. Ketone **12** (Table II) was prepared by diazo transfer[9] to commercially available 7-tridecanone (di-*n*-hexyl ketone). In this case, we do observe that β-hydride elimination is the major competing reaction pathway. The elimination product is purely *Z*, as previously observed by Ganem.[5a]

In the cyclization of **12**, the ligand on the rhodium(II) carboxylate catalyst makes a striking difference. The data suggest that more electron-withdrawing ligands favor β-hydride elimination, while 1,5-insertion is favored by more electron-donating ligands. We speculate that the reaction proceeds through an intermediate Rh/carbene complex that is highly electron deficient at carbon and that this complex is further destabilized by electron-withdrawing ligands. With a less stable (more reactive) intermediate, the entropically less demanding pathway (earlier transition state), β-hydride elimination, will be favored.

An alternative 1,5-insertion product, cyclopentanone **17**, could have been formed from **12**. We have prepared **17** by an independent route and are unable to detect it in the reaction mixture (<1%). This suggests further that the intermediate Rh/carbene complex favors a conformation such as **15a** or **15b**, rather than **15c**.

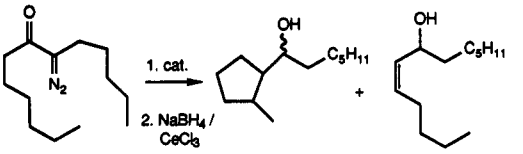


15a 15b 16 15c 17

(8) (a) Short, R. P.; Revol, J.-M.; Ranu, B. C.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 4453. (b) Kennedy, M.; McKervey, M. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1028. (c) Saba, A. *Tetrahedron Lett.* **1990**, *31*, 4657.

(9) For leading references to methods for diazo transfer, see: (a) Regitz, M. *Org. Synth.* **1971**, *51*, 86. (b) Taber, D. F.; Ruckle, R. E., Jr.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077.

Table II. Rh(II)-Catalyzed Reactions of Diazoalkyl Ketone 12

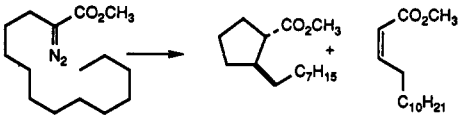


12 13 14

	Rh(II) ligand	yield,[a] %	13, %	14,[b] %
1	$CH_3CO_2^-$	86	70	30
2	$C_6H_5CO_2^-$	83	60	40
3	$(p\text{-Cl})C_6H_4CO_2^-$	81	40	60
4	$CF_3CO_2^-$	87	38	62

[a] Chroamtographed yield of pure cyclized ketones. [b] The enone was pure *Z* by ^1H NMR analysis.

Table III. Rh(II)-Catalyzed Reactions of Diazo Ester 21

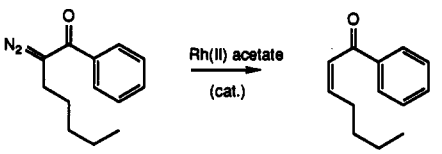


21 22 23

	Rh(II) ligand	yield,[a] %	22, %	23,[b,c] %
1	$(CH_3)_3CCO_2^-$	97	85	15
2	$n\text{-}C_8H_{17}CO_2^-$	90	78	22
3	$C_6H_5CO_2^-$	88	78	22
4	$CH_3CO_2^-$	92	66	34
5	$CF_3CO_2^-$	93	52	48

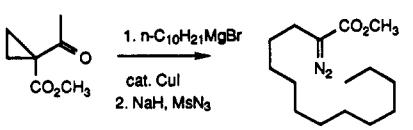
[a] Yield (**22** + **23**) of pure chromatographed material. [b] The alkene was pure *Z* by ^1H NMR analysis. [c] The ratio of **22** to **23** was determined by ^1H NMR analysis of the chromatographed (**22** + **23**) mixture.

We attempted the cyclization of diazo ketone **18** but, with rhodium(II) acetate, received only alkene **19**. We speculate, again, that the benzoyl group, more electron-withdrawing than an alkanoyl group, is destabilizing the organorhodium intermediate, leading to an earlier transition state and a preference for alkene formation.



18 19

Cyclization of an α-Diazo β-Methylene Ester. α-Diazo esters are readily prepared by diazo transfer/fragmentation[9] of α-alkylated β-keto esters. In the case of **21**, we prepared the intermediate β-keto ester by conjugate addition to cyclopropyl ester **20**.[10]

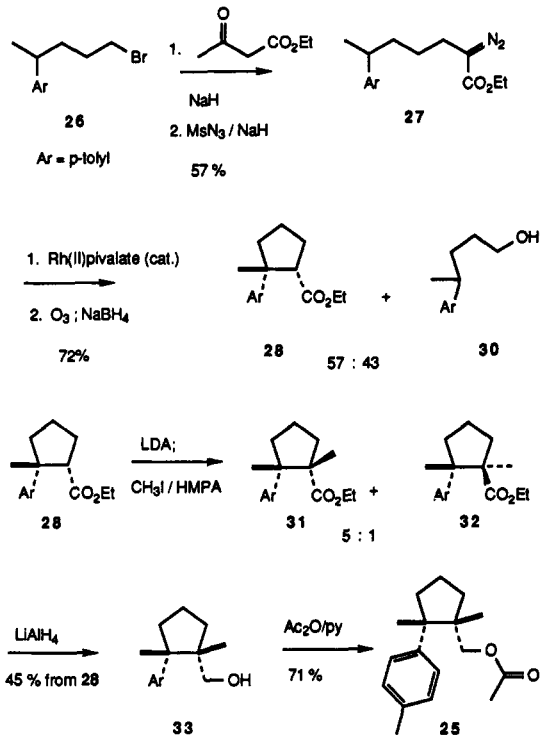


20 21

The results from cyclization of **21** (Table III) parallel the results from diazo ketone **12**. We reasoned, then, that

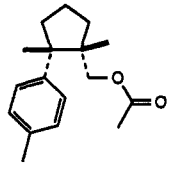
(10) Cyclopropyl ester **20** was prepared by a modification of the literature procedure: Matsumoto, T.; Shirahama, H.; Ichihara, A.; Shin, H.; Kagawa, S.; Hisamitsu, T.; Kamada, T.; Sakan, F. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1136.

Scheme I



if electron-withdrawing ligands favored alkene formation, electron-donating ligands might favor cyclization. In fact, (commercially available) rhodium(II) *n*-octanoate (entry 2) was significantly better than rhodium(II) acetate (entry 4), and rhodium(II) pivalate (entry 1), prepared by a modification of the literature procedure,[11] was better still. Given the ease with which the starting materials are prepared, Rh(II)-catalyzed cyclization of α-diazo esters should be a useful method for the construction of substituted cyclopentane carboxylates. It should be noted that the *kinetic* cyclization product **22** is >95% trans.

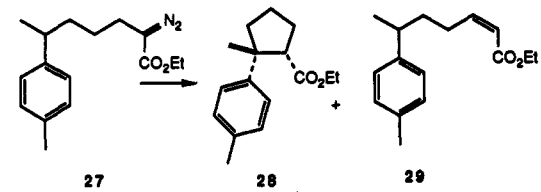
Synthesis of (±)-Tochuinyl Acetate. Tochuinyl acetate **25** was recently isolated[12] from the nudibranch *Tochuina tetraquetra* of Port Hardy, British Columbia. The vicinal quaternary stereogenic centers of **25** offer an intriguing synthetic challenge. We have already established[13] that a single such cyclic quaternary center can be constructed with absolute stereocontrol, as Rh(II)-catalyzed C–H insertion proceeds with retention of absolute configuration. We now report that α-alkylation of the derived cyclopentane carboxylate proceeds with remarkable diastereoselectivity.



25

The starting point for the synthesis is bromide **26** (Scheme I), prepared from the corresponding alcohol **29**.[14,15] Displacement with the anion of ethyl acetoacetate, followed by diazo transfer,[9] gave the desired α-diazo ester **27**.

Table IV. Rh(II)-Catalyzed Cyclization of Diazo Ester 27



27 28 29

	Rh(II) ligand	yield,[a] %	22, %	23,[b,c] %
1	$(CH_3)_3CCO_2^-$	89	55	45
2	$n\text{-}C_8H_{17}CO_2^-$	91	45	55
3	$C_6H_5CO_2^-$	94	42	58
4	$CH_3CO_2^-$	89	37	63
5	$CF_3CO_2^-$	99	26	74

[a] Yield (**28** + **29**) of pure chromatographed material. [b] The alkene was pure *Z* by ^1H NMR analysis. [c] The ratio of **28** to **29** was determined by ^1H NMR analysis of the chromatographed (**28** + **29**) mixture.

Rhodium(II) carboxylate catalyzed insertion into a benzylic C–H is more difficult than insertion into an aliphatic C–H.[3a] It was therefore not surprising that β-hydride elimination competed with cyclization more strongly for **27** (Table IV) than it had with **21** (Table III). Again, the more electron-donating carboxylates more strongly favored cyclopentane formation. It is striking that the *kinetically* formed ester **28** is >95% a single diastereomer. The ethyl ester methylene ^1H NMR chemical shift of 3.72 ppm indicates that the ethoxycarbonyl group in this diastereomer is syn to the vicinal arene ring.

In practice, the crude cyclized product was worked up with ozone followed by sodium borohydride to give (Scheme I) the cyclized ester **28** as a mixture with alcohol **30**. The latter was easily separated and then recycled via bromide **26**.

Alkylation of **28** was effected by anion formation with lithium diisopropylamide in THF, followed by addition of methyl iodide in HMPA. At this point, we were establishing a quaternary center adjacent to an existing quaternary center. Usually, little 1,2-induction would be expected. We were gratified to observe that in this case the one diastereomer dominated (85% of the mixture). This diastereomer had an ester methylene chemical shift of 3.70 ppm, again indicating shielding by the vicinal cis arene. The minor diastereomer (15% of the mixture) had a more typical ester chemical shift of 4.18 ppm.

Reduction of the mixture of esters to give alcohol **33**, followed by acetylation, led to (±)-tochuinyl acetate **25**. The IR and ^1H and ^{13}C NMR spectra of synthetic **25** were identical with those of natural material.[12,16]

Conclusion

It is apparent that rhodium(II) carboxylate catalyzed 1,5 C–H insertion, to form cyclopentanes, can in some cases compete effectively with the alternative β-hydride elimination. In a further development, it is especially noteworthy that diazo esters **21** and **27** cyclize to **22** and **28** as single diastereomers (^{13}C NMR), suggesting a highly or-

(11) Tetrapivalatodirhodium was prepared by exchange of tetrakis(trifluoroacetato)dirhodium with excess pivalic acid: Callot, H. J.; Metz, F. *Tetrahedron* **1985**, *41*, 4495 and references cited therein.
(12) Williams, D. E.; Andersen, R. J. *Can. J. Chem.* **1987**, *65*, 2244.
(13) Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196.
(14) (a) Rupe, H.; Steinbach, A. *Chem. Ber.* **1911**, *44*, 584. (b) Carr, R. V. C.; Williams, R. V.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 4976.
(15) The alcohol **30** has been prepared in enantiomerically pure form: Takano, S.; Goto, E.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 5567. The preparation outlined in this article is also the subject of an industrial patent: *Chem. Abstr.* **1984**, *101*, P151586a.
(16) Anderson, R. J. University of British Columbia, personal communication.

dered transition state. We are currently pursuing the design of enantiomerically pure Rh(II) carboxylates for the cyclization of diazo ester **21**.

Experimental Section[17]

Catalyst Preparation. Rh(II) catalysts were commercially available (acetate, octanoate) or were prepared by published procedures.[11,18]

2-Diazo-3-tetradecanone (9). By the method of Hudlicky,[8] lauroyl chloride (3.26 g, 14.9 mmol) in 20 mL of ether was added dropwise to a mixture of diazoethane (from 5.68 g (48.5 mmol) of *N*-ethyl-*N*-nitrosourea), triethylamine (2 mL), and ether (150 mL) at 0 °C. After an additional 30 min the mixture was filtered through 3 g of 60/200 mesh silica gel with 100 mL of ethyl acetate and concentrated in vacuo. The residue was chromatographed to give 2.9 g (87%) of **9** as a yellow oil: R_f (10% EtOAc/hexane) 0.51; ^{1}H NMR δ 2.45 (t, J = 7.1 Hz, 2 H), 1.94 (s, 3 H), 1.5–1.75 (m, 2 H), 1.1–1.5 (m, 16 H), 0.87 (t, J = 6.4 Hz, 3 H); ^{13}C NMR δ u: 194.7, 61.6, 37.6, 31.8, 29.4, 29.3, 29.21, 29.17, 29.1, 24.7, 22.5, d: 13.9, 7.5; IR 1646, 2067, 2856, 2929, 2958 cm^{-1}.

***trans*-2-Methyl-3-octylcyclopentanone (10) and Bis[2-(3-oxotetradecylidene)diazene] (11).** Diazo ketone **9** (200 mg, 0.84 mmol) in 15 mL of dry CH_2Cl_2 was added dropwise over 0.5 h with stirring to 1 mg of $Rh_2(OAc)_4$ in 5 mL of dry CH_2Cl_2 at rt. After 30 min, the mixture was concentrated and chromatographed directly to yield 40.3 mg of **11** as a yellow oil, followed by 103.7 mg of **10** as a colorless oil. The total yield was 82%, and the ratio of **10**/**11** was 72/23. For **10** (after epimerization with acetic acid and 25% aqueous HCl): R_f (10% EtOAc/hexane) 0.54; ^{1}H NMR δ 1.9–2.4 (m, 4 H), 1.5–1.9 (m, 2 H), 1.2–1.5 (m, 14 H), 1.06 (d, J = 6.5 Hz, 3 H), 0.88 (t, J = 6.4 Hz, 3 H); ^{13}C NMR δ u: 221.9, 37.4, 34.5, 31.8, 29.9, 29.5, 29.3, 27.2, 27.1, 22.6, d: 50.5, 44.8, 14.0, 12.6; IR 2940, 1745 cm^{-1}; MS m/z (relative intensity) 180 (9), 155 (1), 115 (83), 113 (100).

For **11**: R_f (10% EtOAc/hexane) 0.80; ^{1}H NMR δ 2.73 (t, 2 H, J = 7.3 Hz), 2.33 (s, 3 H), 1.45–1.7 (m, 2 H), 1.1–1.45 (m, 16 H), 0.88 (t, J = 6.1 Hz, 3 H); ^{13}C NMR δ u: 199.61, 197.7, 74.4, 35.7, 31.9, 29.6, 29.4, 29.3, 29.1, 23.0, 22.6, d: 23.7, 14.0; IR 1717, 2857, 2873, 2929, 2957 cm^{-1}; MS m/z (relative intensity) 238 (2), 210 (3), 193 (13), 164 (28), 141 (100), 113 (65).

6-Diazo-7-tridecanone (12). Diazo transfer was carried out following our published procedure.[9b] Thus, 200 mg (1.01 mmol) of dihexyl ketone and 222 mg (3.01mmol) of ethyl formate in an additional 2 mL of ether was added dropwise to a mixture of NaH (144 mg, 3.03 mmol of 50% dispersion in mineral oil), one drop of absolute ethanol, and 2 mL of anhydrous ether at 0 °C. After 3 h, the cooling bath was removed, and stirring was continued overnight. Methanesulfonyl azide (363 mg, 3.03 mmol) in 5 mL of ether was then added. After an additional 2 h the reaction mixture was partioned between 10% aqueous NaOH and pentane, and the combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed to give 160 mg (0.714 mmol, 71%) of **12** as a yellow oil: R_f (10% EtOAc/hexane) 0.51; ^{1}H NMR δ 0.88 (t, 6 H), 1.29 (bs, 10 H), 1.47 (m, 2 H), 1.62 (m, 2 H), 2.34 (t, J = 7 Hz, 2 H), 2.43 (t, J = 7 Hz, 2 H); ^{13}C NMR δ d: 14.0 (2), u: 22.4 (2), 22.5, 24.9, 26.7, 28.9, 31.0, 31.6, 38.1, 66.5, 194.6; IR 2959, 2931, 2860, 2064, 1643 cm^{-1}; MS m/z (relative intensity) 196 (27), 167 (50), 126 (60), 125 (31), 113 (100), 112 (55), 111 (95); HRMS (CI, CH_4) calcd for $C_{13}H_{25}N_2O$ 225.1966, obsd 225.196.

2-Methyl-α-(1-hexyl)cyclopentanemethanol (13) and (*Z*)-5-Tridecen-7-ol (14). Diazo ketone **12** (100 mg, 0.44 mmol) in 4 mL of dry CH_2Cl_2 was added dropwise over 0.5 h with stirring to 1 mg of $Rh_2(OAc)_4$ in 4 mL of dry CH_2Cl_2 at rt. After 30 min, the mixture was concentrated and chromatographed directly to yield 75 mg (86%) of a mixture of cyclized (**16**) and eliminated ketones.

Following the procedure of Luche,[19] $NaBH_4$ (15 mg, 0.4 mmol) was added to a solution of $CeCl_3$ (135 mg, 0.38 mmol), methanol (1 mL), and the above ketone mixture. After 15 min, the reaction mixture was concentrated and chromatographed to yield of 37 mg of **13** as a colorless oil, followed by 16 mg of **14** as a colorless oil.

For **13**: R_f (10% EtOAc/petroleum ether) 0.54; ^{1}H NMR δ 3.58 (m, 0.5 H), 3.45 (t, J = 6.7 Hz, 0.5 H), 1.6–1.9 (m, 4 H), 1.1–1.6 (m, 15 H), 1.04 (d, J = 6.5 Hz, 1.5 H), 0.98 (d, J = 6.5 Hz, 1.5 H), 0.8 (t, J = 7.0 Hz, 3 H); ^{13}C NMR δ d: 76.0, 72.3, 53.2, 52.75, 36.0, 22.1, 19.8, 14.1, u: 36.4, 35.6, 35.5, 35.3, 31.9), 29.8, 29.4, 26.2, 25.9, 24.8, 24.1, 22.7; IR 3628, 2861, 2871, 2931, 2955, 1460 cm^{-1}; MS m/z (relative intensity) 197 (0.3), 180 (9), 155 (0.6), 137 (0.6), 115 (37), 113 (100).

For **14**: R_f (10% EtOAc/petroleum ether) 0.36; ^{1}H NMR 5.55 (m, 2 H), 4.55 (m, 1 H), 2.1–2.3 (m, 2 H), 1.2–1.8 (m, 15 H), 0.8–1.1 (m, 6 H); ^{13}C NMR δ d: 132.6, 132.3, 67.7, 14.1, 13.9, u: 37.5, 31.8, 29.3, 27.4, 25.4, 22.6, 22.3; IR 3622, 2860, 2833, 2960, 3622, 1460 cm^{-1}; MS m/z (relative intensity) 198 (0.3), 180 (1), 155 (3), 128 (6), 123 (3), 113 (100).

Methyl 1-(1-Oxoethyl)cyclopropanecarboxylate (20). In an improvement of the literature procedure[10] a mixture of methyl acetoacetate (20 mL, 185 mmol), 1,2-dibromoethane (24 mL, 278 mmol), K_2CO_3 (76.8 g, 556 mmol), and 186 mL of acetone was stirred mechanically and maintained at relux for 24 h. The mixture was filtered with ether, concentrated, and distilled through a 10-cm Vigreaux column at 30 Torr to give **20** as a colorless oil, bp. 85–95 °C (19.0 g, 72% based on methyl acetoacetate): R_f (10% EtOAc/petroleum ether) 0.40; ^{1}H NMR δ 3.75 (s, 3 H), 2.47 (s, 3 H), 1.48 (s, 4 H); ^{13}C NMR δ u: 202.8, 171.4, 49.7, 19.1, d: 52.1, 29.7; IR 3011, 2957, 2361, 2342, 1733, 1702, 1439, 1361, 1201, 1124 cm^{-1}; MS m/z (relative intensity) 142 (28), 127 (100), 111 (78), 110 (74), 100 (12); HRMS calcd for $C_7H_{10}O_3$ 142.062 98, obsd 142.0630.

Methyl 2-Diazotetradecanoate (21). The Grignard reagent prepared from 1-bromodecane (16.1 g, 65.6 mmol) and magnesium (1.6 g, 65.6 mmol) in 100 mL of THF was cooled to −20 °C. CuBr·dimethyl sulfide (1.36 g, 6.6 mmol) was added, followed by ester **20** (7.8 g, 54.6 mmol) in 42 mL of THF over 20 min. The mixture was allowed to warm for 1 h then partioned between ether and, sequentially, saturated aqueous NH_4Cl and brine. The organic layers were dried ($MgSO_4$), concentrated, and chromatographed to yield the homologated β-keto ester as a colorless oil (7.8 g, 50% yield from **20**): R_f (5% EtOAc/petroleum ether) 0.40; ^{1}H NMR 3.78 (s, 3 H), 3.47 (t, J = 7.4 Hz, 1 H), 2.27 (s, 3 H), 1.89–1.87 (m, 2 H), 1.30 (bs, 20 H), 0.93 (t, J = 6.6 Hz, 3 H); ^{13}C NMR δ u: 203.3, 170.4, 31.9, 29.61, 29.56, 29.48, 29.29, 28.2, 27.4, 22.6, d: 59.7, 52.3, 28.7, 14.1; IR 2927, 2855, 1747, 1720, 1466, 1436, 1359, 1245, 1151 cm^{-1}; MS m/z (relative intensity) 242 (26), 199 (7), 143 (12), 129 (29), 117 (25), 116 (100); HRMS calcd for $C_{17}H_{32}O_3$ 284.235 13, obsd 284.2338.

NaH (60% in mineral oil, 225 mg, 5.6 mmol) was washed three times with petroleum ether, then suspended in 0.8 mL of ether at 0 °C. The β-keto ester from above (1.1 g, 3.7 mmol) in 3 mL of ether was added dropwise. After 10 min, methanesulfonyl azide (1.37 g, 11.3 mmol) in 1.0 mL of ether was added. After 1.5 h (ice bath slowly melts), the reaction was partioned between ether and 10% aqueous NaOH. The organic layers were dried ($MgSO_4$), concentrated, and chromatographed to give the α-diazo ester **21** as a yellow oil (0.870 g, 87% yield, 44% overall yield from cyclopropane **20**): R_f (5% EtOAc/petroleum ether) 0.58; ^{1}H NMR δ 3.76 (s, 3 H), 2.30 (t, 2 H, J = 7.4 Hz), 1.53–1.44 (m, 2 H), 1.26 (s, 20 H), 0.88 (t, J = 6.6 Hz, 3 H); ^{13}C NMR δ u: 168.0, 31.9, 29.6, 29.5, 29.3, 29.2, 29.0, 28.7, 27.5, 23.0, 22.6, d: 51.8, 14.0; IR 2925, 2857, 2081, 1702, 1698, 1438, 1352, 1305, 1192, 1136 cm^{-1}; MS m/z (relative intensity) 127 (16), 114 (9), 113 (94), 101 (13), 100 (29), 87 (100); HRMS calcd for $C_{15}H_{28}O_2N_2$ 268.215 06 (240.208 92 loss N_2), obsd 240.2095.

Methyl *trans*-2-Octylcyclopentanecarboxylate (22) and Methyl (*Z*)-2-Tetradecenoate (23). Diazo ester **21** (611 mg, 2.3 mmol) in 9 mL of dry CH_2Cl_2 was added dropwise over 15 min with stirring to <1 mg of tetrapivalatodirhodium in 13.6 mL of dry CH_2Cl_2 at rt. After 30 min, the mixture was concentrated and chromatographed directly to yield 532 mg (97% yield) of a mixture of cyclized and eliminated esters (85:15 by ^{1}H NMR integration).

This mixture (527 mg, 2.2 mmol) in 1:2 CH_2Cl_2/CH_3OH containing a drop of pyridine was treated with a stream of ozone in

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oxygen at −78 °C until a faint blue color persisted. The mixture was flushed with N_2, then $NaBH_4$ (166 mg, 4.4 mmol) was added and the cooling bath was removed. After 1.5 h the reaction mixture was concentrated and chromatographed directly to yield ester **22** (402 mg, 74% yield from the diazo ester **21**) as a colorless oil, followed by 1-dodecanol from cleavage of **23** (73 mg, 13% from **21**), also as a colorless oil.

22: R_f (5% EtOAc)/petroleum ether) 0.67; ^{1}H NMR 3.67 (s, 3 H), 2.31 (q, J = 8.3 Hz, 1 H), 1.98 (m, 1 H), 1.93–1.70 (m, 2 H), 1.68–1.62 (m, 2 H), 1.60–1.15 (bs, 16 H), 0.88 (t, J = 6.4, 3 H); ^{13}C NMR δ u: 177.3, 35.4, 32.6, 31.9, 30.4, 29.8, 29.6, 29.3, 28.2, 24.8, 22.7, d: 51.5, 50.4, 44.5, 14.1; IR 2955, 2927, 2856, 1737, 1458, 1435, 1376, 1262, 1196, 1159 cm^{-1}; MS m/z (relative intensity) 240 (7), 128 (10), 127 (100), 100 (3); HRMS calcd for $C_{15}H_{28}O_2$ 240.20892, obsd 240.2059.

1-Bromo-4-(4-methylphenyl)pentane (26). CBr_4 (5.48 g, 16.5 mmol) was added to triphenylphosphine (4.33 g, 16.5 mmol) and α,4-dimethylbenzenebutanol (**30**)[14] (1.223 g, 6.86 mmol) in 17 mL of ether at 0 °C. The cooling bath was removed, and stirring was continued for 18 h. Petroleum ether (25 mL) was added to precipitate triphenylphosphine oxide. The supernatant was concentrated, then distilled bulb-to-bulb at 5 Torr (bp bath 110–130 °C) to give bromide **26** as a colorless oil (1.26 g, 76% yield): TLC R_f (5% EtOAc/petroleum ether) 0.78; ^{1}H NMR δ 7.11 (d, J = 8.2 Hz, 2 H), 7.08 (d, J = 8.2 Hz, 2 H), 3.34 (t, J = 6.3 Hz, 2 H), 2.65 (m, 1 H), 2.32 (s, 3 H), 1.87–1.60 (m, 4 H), 1.24 (d, J = 6.9 Hz, 3 H); ^{13}C NMR δ u: 143.8, 135.5, 36.8, 34.0, 31.0, d: 129.1, 126.8, 38.9, 22.5, 21.0; IR 3006, 2961, 2925, 2870, 1515, 1454, 1246, 1020, 816 cm^{-1}; MS m/z (relative intensity) 242 (23), 240 (25), 120 (61), 119 (100), 118 (12), 117 (25), 115 (14), 105 (46), 103 (11); HRMS calcd for $C_{12}H_{17}Br$ 240.0513, obsd 240.0496.

Ethyl ε-Diazo-α,4-dimethylbenzenehexanoate (27). NaH (60% in mineral oil, 0.38 g, 9.5 mmol) was rinsed three times with petroleum ether, then suspended in 1.0 mL of DME and cooled to 0 °C. Ethyl acetoacetate (1.25 mL, 9.8 mmol) was added dropwise to give a solid mass. Bu_4NI (0.183 g, 0.5 mmol) was added, followed by bromide **26** (1.18 g, 4.88 mmol) in 4 mL of DME, and the reaction was stirred at 80 °C for 18 h. The reaction mixture was partioned between ether and 5% aqueous HCl. The organic layers were dried ($MgSO_4$), concentrated, and chromatographed to give the alkylated β-keto ester as a colorless oil (1.0 g, 70% yield): R_f (5% EtOAc/petroleum ether) 0.28; ^{1}H NMR 7.06 (dd, 4 H, J = 8.2 Hz, 5.0), 4.15 (q, 2 H, J = 7.1 Hz), 3.33 (t, 1 H, J = 7.4), 2.61 (sex., 1 H, J = 21 Hz), 2.31 (s, 3 H), 2.13 (s, 3 H), 1.94–1.67 (m, 2 H), 1.57 (q, 2 H), 1.26–1.19 (m, 8 H); ^{13}C NMR δ u: 203.2, 169.9, 144.2, 135.3, 61.2, 38.0, 28.2, 25.5, d: 129.0, 126.8, 59.8, 39.2, 39.1, 28.7, 28.6, 22.4, 20.9, 14.0; IR 3047, 2959, 2927, 2868, 1720, 1716, 1515, 1460, 1358, 1151, 1022, 818 cm^{-1}; MS m/z (relative intensity) 290 (6), 272 (7), 198 (8), 158 (26), 146 (20), 145 (48), 143 (24), 132 (10), 131 (7), 120 (34), 119 (100), 117 (20), 105 (22); HRMS calcd for $C_{18}H_{26}O_3$ 290.18818, obsd 290.1881.

NaH (60% in mineral oil, 0.156 g, 3.9 mmol) was washed three times with petroleum ether then suspended in 0.2 mL ether at 0 °C. The β-keto ester from above (0.734 g, 2.5 mmol) in 2.0 mL of ether was added dropwise. After 10 min, methanesulfonyl azide (0.896 g, 7.4 mmol) in 1.0 mL of ether was added. After 18 h (ice bath slowly melts), the reaction was partioned between ether and 10% aqueous NaOH. The organic layers were dried ($MgSO_4$), concentrated, and chromatographed to give the α-diazo ester **27** as a yellow oil (0.569 g, 57% yield from bromide **26**): R_f (5% EtOAc/petroleum ether) 0.40; ^{1}H NMR 7.10 (d, J = 8.2, 2 H), 7.05 (d, J = 8.2 Hz, 2 H), 4.20 (q, 2 H, J = 7.2 Hz), 2.65 (m, 1 H), 2.32 (s, 3 H), 2.26 (t, 2 H, J = 7.4 Hz), 1.66–1.56 (m, 2 H), 1.48–1.30 (m, 2 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.23 (d, J = 7.0 Hz, 3 H); ^{13}C NMR δ u: 167.7, 144.0, 135.4, 60.6, 37.4, 25.7, 23.0, d: 129.1, 126.8, 39.2, 22.4, 21.0, 14.5; IR 3020, 2928, 2080, 1694, 1515, 1460, 1394, 1371, 1129, 816 cm^{-1}; MS m/z (relative intensity) 246 (2), 185 (4), 173 (54), 172 (16), 158 (10), 157 (14), 146 (13), 145 (13), 133 (22), 132 (20), 119 (100), 114 (34), 105 (22), 101 (7); HRMS calcd for $C_{16}H_{22}O_2N_2$ 274.16811 (246.16197 loss N_2), obsd 246.1579.

Ethyl 2-Methyl-2-(4-methylphenyl)cyclopentanecarboxylate (28) and α,4-Dimethylbenzenebutanol (30). Diazo ester **27** (528 mg, 1.92 mmol) in 7.6 mL of dry CH_2Cl_2 was added dropwise over 10 min with stirring to <1 mg of tetrapivalatodirhodium in 11.6 mL of dry CH_2Cl_2 at rt. After 30 min, the mixture was concentrated and chromatographed directly to yield 443 mg (93%) of a mixture of cyclized and eliminated esters.

This mixture in 1:2 CH_2Cl_2/CH_3OH containing one drop of pyridine was treated with a stream of ozone in oxygen at −78 °C until a faint blue color persisted. The mixture was flushed with N_2, and then $NaBH_4$ (142 mg, 3.75 mmol) was added and the cooling bath was removed. After 1.5 h the reaction mixture was concentrated and chromatographed directly to yield ester **28** (196 mg, 41% from **27**) as a colorless oil, followed by alcohol **30** (151 mg, 44% from **27**), also as a colorless oil.

28: R_f (5% EtOAc/petroleum ether) 0.53; ^{1}H NMR 7.18 (d, J = 8.2 Hz, 2 H), 7.06 (d, J = 8.2 Hz, 2 H), 3.72 (m, 2 H), 2.90 (m, 1 H), 2.48 (m, 1 H), 2.29 (s, 3 H), 2.12–1.78 (m, 5 H), 1.36 (s, 3 H), 0.90 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ u: 175.2, 135.2, 59.6, 50.8, 37.3, 28.2, 22.6, d: 128.8, 128.5, 126.4, 55.7, 30.4, 20.9, 13.8; IR 3024, 2966, 1732, 1516, 1446, 1372, 1346, 1160, 1094, 816 cm^{-1}; MS m/z (relative intensity) 246 (40), 173 (43), 172 (41), 158 (19), 157 (28), 146 (94), 145 (22), 143 (30), 132 (37), 131 (49), 129 (12), 128 (12), 119 (33), 117 (15), 115 (15), 105 (28), 101 (100); HRMS calcd for $C_{16}H_{22}O_2$ 246.16197, obsd 246.1638.

30: R_f (20% EtOAc/petroleum ether) 0.20; ^{1}H NMR δ 7.11 (H, d, J = 8.6 Hz, 2 H), 7.07 (d, J = 8.6 Hz, 2 H), 3.58 (t, J = 6.3, 2 H), 2.65 (sex., J = 7.0 Hz, 1 H), 2.31 (s, 3 H), 1.72–1.32 (m, 4 H), 1.24 (d, J = 7.0 Hz, 3 H); ^{13}C NMR δ u: 144.2, 135.3, 63.0, 34.4, 31.0, d: 129.0, 126.8, 39.3, 22.5, 21.0; IR 3337, 2935, 2870, 1515, 1455, 1376, 1060, 1025, 816 cm^{-1}; MS m/z (relative intensity) 178 (21), 145 (11), 119 (100), 117 (10), 105 (10); HRMS calcd for $C_{12}H_{18}O$ 178.13576, obsd 178.1332.

(1*R,2*S**)-1,2-Dimethyl-2-(4-methylphenyl)cyclopentanemethanol (33).** Ester **28** (192 mg, 0.78 mmol) in THF (1.4 mL) was added dropwise to LDA (0.34 mL diisopropylamine and 0.92 mL of 2.55 M n-BuLi/hexane) in 4.6 mL of THF at −78 °C. After 30 min, CH_3I (0.17 mL, 2.7 mmol) in HMPA (0.27 mL) was added. After 75 min (cooling bath slowly warms), the reaction mixture was partioned between ether and, sequentially, 5% aqueous HCl, 10% aqueous $NaHSO_3$, and brine. The organic layers were dried ($MgSO_4$), concentrated, and chromatographed to give the alkylated ester (160 mg, 79% yield). The ester was a mixture of diastereomers **31** and **32** in about a 5:1 ratio, as indicated by a minor ethyl ester at 4.08 ppm, and a major ethyl diastereomer at 3.70 ppm.

The mixture of esters (60 mg, 0.23 mmol) in 0.5 mL of THF was added dropwise to $LiAlH_4$ (25 mg, 0.67 mmol) in 0.25 mL of THF at 0 °C. The mixture was warmed to 70 °C (sealed reaction vial) for 2.5 h, then cooled and quenched by sequential addition of water (1 drop), 10% aqueous NaOH (1 drop), and water (3 drops). The reaction mixture was diluted with ether, dried ($MgSO_4$), concentrated, and chromatographed to yield alcohol **33** as a colorless oil (29 mg, 45% yield from the unalkylated ester **28**): R_f (20% EtOAc/petroleum ether) 0.61; ^{1}H NMR δ 7.28 (d, J = 8.1 Hz, 2 H), 7.11 (d, J = 8.1 Hz, 2 H), 3.08 (dd, J = 2.9, 11.2 Hz, 1 H), 3.03 (d, J = 2.9 Hz, 1 H), 2.50–2.42 (m, 1 H), 2.31 (s, 3 H), 1.88–1.65 (m, 4 H), 1.59–1.48 (m, 1 H), 1.30 (s, 3 H), 1.11 (s, 3 H), 0.88 (bs, 1 H); ^{13}C NMR δ u: 143.4, 135.4, 69.3, 49.4, 49.2, 37.4, 34.8, 20.2, d: 128.8, 126.6, 25.0, 20.7, 19.3; IR 3381, 3026, 2962, 2878, 1515, 1454, 1378, 1021, 813 cm^{-1}; MS m/z (relative intensity) 218 (24), 145 (47), 143 (12), 135 (20), 132 (85), 131 (24), 119 (100), 105 (30); HRMS calcd for $C_{15}H_{22}O$ 218.16706, obsd 218.1662. Anal. Calcd for $C_{15}H_{22}O$: C, 80.85; H, 10.18. Found C, 81.08; H, 9.90.

(±)-Tochuinyl Acetate (25). Alcohol **33** (24 mg, 0.11 mmol) was dissolved in 0.05 mL of pyridine and 0.05 mL of acetic anhydride. After 18 h the reaction mixture was partioned between ether and, sequentially, 5% aqueous HCl and 5% aqueous NaOH. The organic layers were dried ($MgSO_4$), concentrated, and chromatographed to yield (±)-tochuinyl acetate (**25**) as a colorless oil (20 mg, 71% yield): R_f (5% EtOAc/petroleum ether) 0.44; ^{1}H NMR δ 7.22 (d, J = 8.2 Hz, 2 H), 7.08 (d, J = 8.2 Hz, 2 H), 3.59 (d, J = 11.0 Hz, 1 H), 3.35 (d, J = 11.0 Hz, 1 H), 2.49 (m, 1 H), 2.30 (s, 3 H) 1.93 (s, 3 H), 1.90–1.68 (m, 4 H), 1.55 (m, 1 H), 1.33 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR δ u: 170.9, 143.1, 135.3, 70.6, 50.0, 47.5, 37.7, 35.0, 20.2, d: 128.6, 126.8, 25.1, 20.7, 19.6; IR 3027, 2966, 2880, 1743, 1515, 1479, 1467, 1463, 1378, 1239, 1033, 813 cm^{-1}; MS m/z (relative intensity) 260 (31), 185 (6), 158 (21), 145 (18), 133 (6), 132 (45), 119 (26), 84 (100); HRMS calcd for $C_{17}H_{24}O_2$ 260.1775, obsd 260.1754. This material was identical (superimposable ^{1}H, ^{13}C NMR, IR) with natural material.[16]

Acknowledgment. We thank Professor R. J. Anderson for providing ^1H, ^{13}C, and IR spectra of natural tochuinyl acetate and The Center for Catalytic Science and Technology of the University of Delaware for financial support. We thank Professor Michael P. Doyle for many helpful comments and suggestions.

Supplementary Material Available: ^1H and ^{13}C NMR spectra of **20–22, 25–28, 30,** and **33** (20 pages). Ordering information is given on any current masthead page.

Enantioselective Rh-Mediated Synthesis of (−)-PGE_2 Methyl Ester

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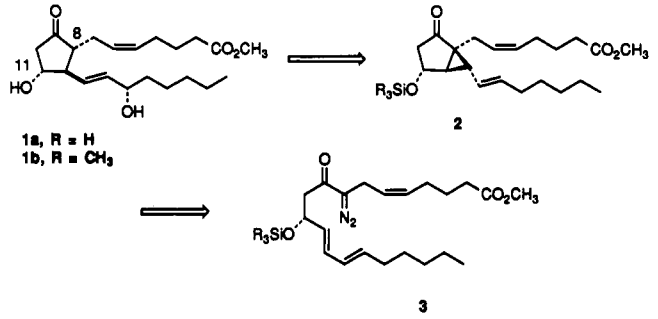
Intramolecular Rh(II) carboxylate catalyzed cyclization of an α-diazo β-methylene ketone to form a fused cyclopropane is shown to compete efficiently with β-hydride elimination, so long as a catalyst derived from an electron-donating carboxylate is used. Cyclization of diazoketone **3** gives **2**, which on opening with thiophenol followed by oxidative rearrangement gives PGE_2 methyl ester **1**. Prostaglandins having the 8-β configuration, recently identified as being physiologically important, can also be prepared using this approach.

Introduction

The prostaglandins are a family of mammalian hormones derived from the essential fatty acids.[1] Prostaglandin E_2 (**1a**), which could be considered the parent of



this series, possesses a wide array of biological activity, including blood platelet aggregation, relaxation of smooth muscle, and inflammatory action.[2]

The intense interest in the biological activity of the prostaglandins has led to extensive synthetic investigations.[3,4] Most synthetic routes to the prostaglandins depend on addition of the two side chains sequentially to a preformed cyclopentane ring, necessitating a resolution step of some sort or a separation of product diastereomers.

Scheme I. Preparation of Silyloxy Acid 10

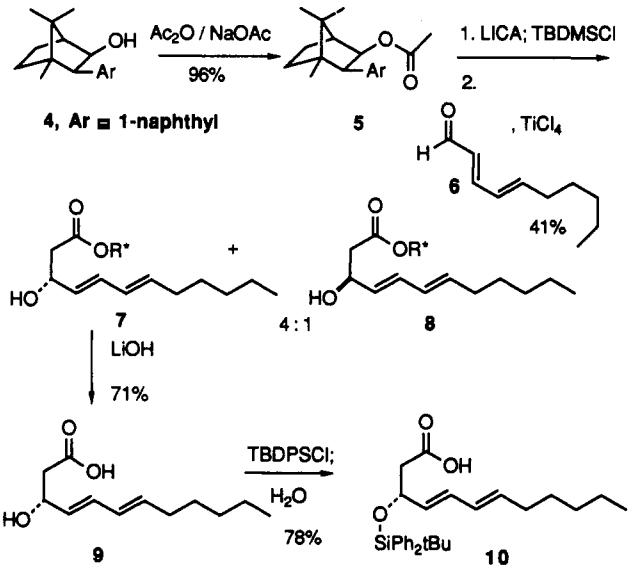
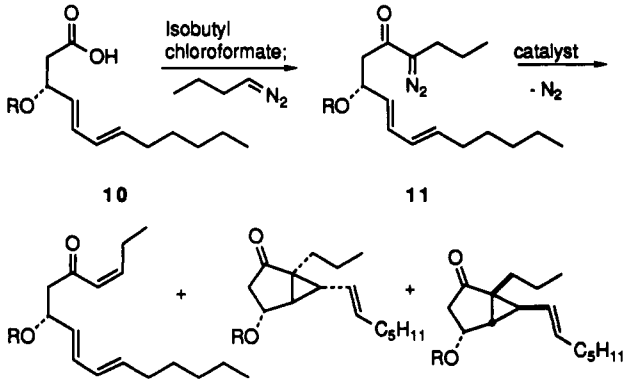


Table I. 1,5-Insertion vs β-Hydride Elimination



catalyst	12	13	14	yield (%)
$Rh_2(CF_3CO_2)_4$	100			90
$Rh_2(C_6H_5CO_2)_4$	14	60	26	84
$Rh_2(CH_3CO_2)_4$		72	28	55
$Cu(TBS)_2$		53	47	78

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