Preparation of a *cis*-Isoprostane Synthon

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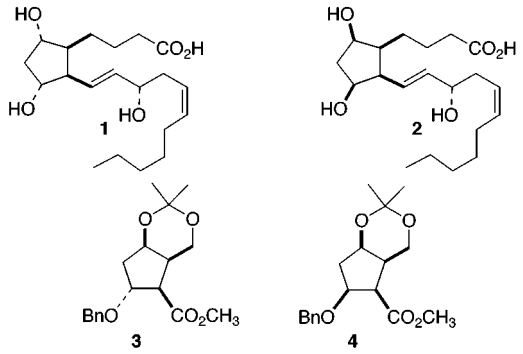
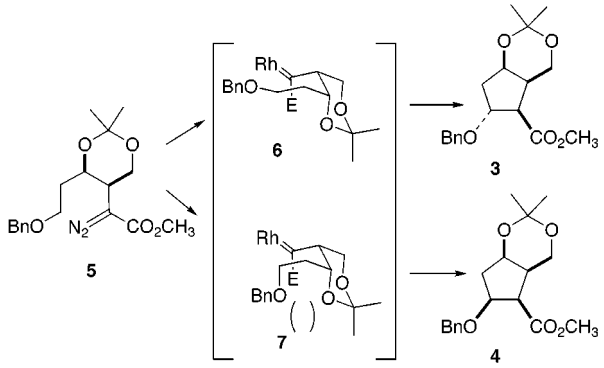
Introduction

Isoprostanes, a new family of eicosanoids, were discovered in humans in 1990.[1] They are generated in vivo independent of the cyclooxygenase enzymes by free-radical mediated oxidation of arachidonic acid. While the physiological importance of the isoprostanes is still under investigation, it has already been demonstrated that endogenously produced isoprostanes are responsible for the kidney failure and subsequent death associated with oxidative liver disease.[2] Both trans- and cis-isoprostanes, exemplified by 12-F_{2t}-isoprostane (**1**) and 12-F_{2c}-isoprostane (**2**) are formed in vivo. While stereodivergent routes to the trans[3] isoprostanes have been described, the routes described to the cis isoprostanes[4] have largely relied on enantiomerically pure percursors. The isoprostanes are formed in vivo in racemic form, and studies of their physiological activity will require the preparation of *both* enantiomers. We have therefore developed a route to the diastereomerically pure, but racemic, cis synthon **4**, as a general precursor to the cis isoprostanes.



Based on previous analyses,[5,6] we hypothesized that the two most likely competing transition states for rhodium-mediated cyclization of diazo ester **5** would be **6** and **7**. In the transition states depicted, the Rh catalyst is equatorial on the forming ring.



To prepare the diazoester **5**, we coupled[7] cinnamyl chloride with propargyl alcohol, then hydrogenated[8] the resulting alkyne **8** to give diene **9**, as shown in Scheme 1. Epoxidation of the diene with *tert*-butyl hydroperoxide and vanadylacetylacetonate gave the epoxide **10**. The opening of **10** with lithioacetonitrile showed remarkable selectivity for addition at the 2-position, leading to the 1,3-diol.[9,10] Protection of the 1,3-diol with 2,2-dimethoxypropane gave the acetonide **11**. Ozonolysis of the

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(2) (a) Banerjee, M.; Kang, K. H.; Morrow, J. D.; Roberts, J. D., II; Newman, J. H. *Am. J. Physiol.* (*Heart Circ. Physiol. 32*) **1992**, *263*, H660. (b) Morrow, J. D.; Moore, K. P.; Awad, J. A.; Ravenscraft, M. D.; Marini, G.; Badr, K. F.; Williams, R.; Roberts, L. J., II. *J. Lipid Mediators* **1993**, *6*, 417.

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(6) Structural optimizations were carried out using Mechanics as provided on the Oxford Scientific CAChe Workstation. CAChe uses an augmented version of Allinger's MM2 force field.

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(8) (a) Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226. (b) Brown, C. A.; Ahuja, V. K.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

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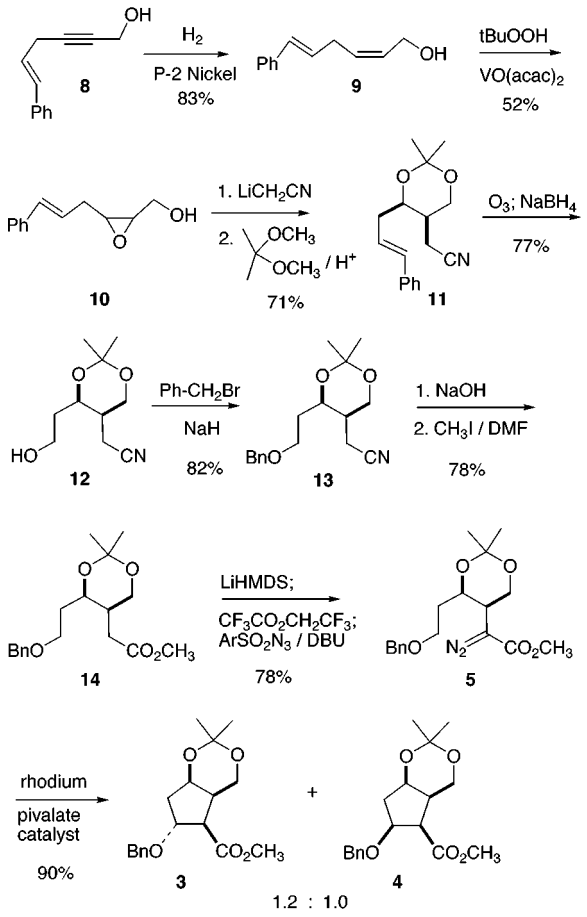
Scheme 1



styrene double bond of **16** followed by reduction led to the alcohol **12**, which was benzylated to give the ether **13**. Hydrolysis followed by esterification[11] then gave the ester **14**.

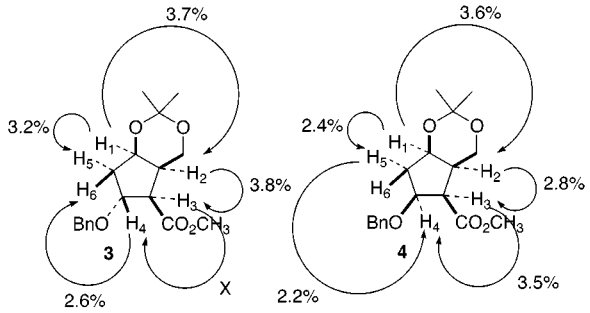
Diazo transfer was accomplished by a combination of our procedure[12] with that of Danheiser.[13] Thus, the ester enolate was first added to trifluoroethyl trifluoroacetate, then the crude trifluoroacetylated product was reacted with DBU and *p*-nitrobenzenesulfonyl azide to give the diazo ester **5**. We have found that this modified procedure works more efficiently with sterically congested esters than the benzoylation method we had previously reported.[12]

In the event, cyclization of **5** with catalytic Rh(II) pivalate (CH_2Cl_2, rt) gave the diastereomeric esters **3** and **4** in a ratio of 1.2:1. The relative configurations of **3** and **4** were assigned by COSY and NOE experiments. In ester **3**, a 3.7% NOE between H_1 and H_2 confirmed the cis ring fusion. The 3.8% NOE between H_2 and H_3 demonstrated

Table 1. Results of Cyclization of Diazoester 5

entry	Rh cat	reaction temp (°C)	yield (%)	ratio (**3**/**4**)
1	$Rh_2(piv)_4$	−78	87	1:1.2
2	$Rh_2(piv)_4$	rt	90	1.2:1
3	$Rh_2(oct)_4$	−78	90	2.6:1
4	$Rh_2(oct)_4$	rt	80	2.8:1
5	$Rh_2(OAc)_4$	rt	83	3:1
6	$Rh_2(TFA)_4$	rt	74	6.4:1
7	$Rh_2(MEPY)_4$	60	77	4.3:1
8	$Rh_2(TPA)_4$	rt	91	1:6.5
9	$Rh_2(TPA)_4$	−78	87	1:6.8

the two alkyl substuents on the cyclopentane ring were cis one to another. The *lack* of an NOE between H_3 and H_4 suggested that the benzyloxy group was exo on the bicyclic system. This was confirmed by an NOE of 3.2% between H_1 and H_5, and an NOE of 2.6% between H_4 and H_6. In ester **4**, the NOE's between NOE between H_1 and H_2 and between H_2 and H_3 demonstrated the same stereochemical relationship as ester **3**. The relative configuration of the benzyloxy group was confirmed by an NOE of 3.5% between H_3 and H_4.



The nearly one-to-one ratio of **3** to **4** was surprising, given the expected steric preference for cyclization to **3**.[14] We hypothesized that the competing transition state in which the benzyloxy group is axial (**7**) might be electronically preferred, the improved overlap of the nonbonding electrons on the oxygen with the target C--H bond making the latter more reactive toward the electrophilic Rh carbene. We further hypothesized that with rhodium pivalate, the steric and electronic factors were just balanced, so **3** and **4** were formed in nearly equal amounts.

We reasoned that if such were the case, then rhodium complexes that gave *more* reactive carbenes might show *improved* selectivity in the reaction. Just the opposite effect has usually been observed,[14] with more reactive rhodium carbenes showing poorer diastereoselectivity. Indeed (Table 1), rhodium catalysts that are known[15] to give more reactive (and, usually, less selective) carbenes in fact show *increased* selectivity in the cyclization of **5**. The cyclization yields dropped off slightly with those catalysts that gave the most reactive carbenes, as with those catalysts products from β-H elimination[16] were formed also. Reaction temperature had a modest influence on the diastereoselectivity of the cyclization. Although the Doyle rhodium carboxamide catalysts[5b,g] have sometimes been found to be stereochemically comple-

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(10) The 1,2-diol was less than 10% of the total product. We were not able to isolate it.

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(12) Taber, D. F.; You, K.; Song, Y. *J. Org. Chem.* **1995**, *60*, 1093.

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(14) Taber, D. F.; Song, Y. *J. Org. Chem.* **1996**, *61*, 6706.

(15) Doyle has also observed a preference for the cis diastereomer from Rh-mediated C−H insertion α to an ether: Doyle, M. P.; Kalinin, A. V. *Tetrahedron Lett.* **1996**, *37*, 1371.

(16) (a) Taber, D. F.; Hennessy, M. J.; Louey, J. P. *J. Org. Chem.* **1992**, *57*, 436. (b) Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **1998**, *63*, 3717.

mentary to the rhodium carboxylates, $Rh_2[(5R)\text{-MEPY}]_4$ also showed a marked preference for the trans diastereomer.

Reasoning that rhodium pivalate, the most sterically demanding of the rhodium carboxylates employed, had given the highest fraction of cis product, we then tried the cyclization with the even more sterically demanding rhodium triphenylacetate.[17] We were delighted to observe that with this catalyst, the all-cis **3** was the dominant product from the cyclization. Again, lower reaction temperature modestly improved the diastereoselectivity of the cyclization.

In **9**, we have found a diazo ester in which steric and electronic demands are very closely balanced. By tuning the electronic demands of the intermediate Rh carbenes, we can make either **3** or **4** the preferred product from the cyclization. It is especially noteworthy that in this system, rhodium complexes that give more reactive intermediate carbenes show *improved* diastereoselectivity in the cyclization. We expect that **4** will be a useful synthon for the preparation of the cis isoprostanes.

Experimental Section[18]

Alkyne 8. To propargyl alcohol (0.50 g, 8.95 mmol) and cinnamyl chloride (1.64 g, 10.7 mmol) in acetone (30 mL) was added potassium carbonate (2.48 g, 17.9 mmol), sodium iodide (2.68 g, 17.9 mmol), copper iodide (1.71 g, 8.95 mmol) and heptane (1.31 mL). After 48 h at rt, the mixture was partitioned between saturated aqueous NH_4Cl and MTBE. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give **8** (1.30 g, 7.55 mmol, 84%) as a pale yellow oil: TLC R_f (20% MTBE/petroleum ether) = 0.19; ^{1}H NMR δ 2.26 (s, 1H), 3.12−3.17 (m, 2H), 4.30 (t, J = 2.0 Hz, 2H), 6.14 (dt, J = 15.7 Hz, 5.7 Hz, 1H), 6.61 (d, J = 15.7 Hz, 1H), 7.18−7.37 (m, 5H); ^{13}C NMR δ u 136.8, 82.9, 80.6; 51.1, 22.2; d 131.3, 128.4, 127.3, 126.1, 123.8; IR (cm^{-1}) 3346, 1495, 1448, 1416, 1135, 1010, 965, 732, 692; MS *m/z* 172 (87), 154 (68), 153 (100), 141 (83); HRMS calcd for $C_{12}H_{14}O$ 172.0888, obsd 172.0888.

Diene 9. To nickel(II) acetate tetrahydrate (0.29 g, 1.17 mmol) in methanol (10.0 mL) was added sodium borohydride (0.07 g, 1.83 mmol). The resulting black solution was evacuated, then maintained under an H_2 atmosphere. Ethylenediamine (0.65 mL) and **8** (1.26 g, 7.32 mmol) in a little methanol were added quickly. The reaction flask was evacuated, then maintained under an H_2 atmosphere. After 24 h, the solvent was evaporated and the residue was partitioned between MTBE and, sequentially, saturated aqueous NH_4Cl and saturated brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give **9** (1.06 g, 6.07 mmol, 83%) as a pale yellow oil: TLC R_f (20% MTBE/petroleum ether) = 0.17; ^{1}H NMR δ 1.54 (s, 1H), 3.00 (t, J = 6.4 Hz, 2H), 4.26 (d, J = 4.3 Hz, 2H), 5.58−5.78 (m, 2H), 6.18 (dt, J = 15.9 Hz, 6.4 Hz, 1H) 6.40 (d, J = 15.9 Hz, 1H), 7.16−7.39 (m, 5H); ^{13}C NMR δ u 137.4, 58.5, 30.8; d 130.5, 129.8, 129.7, 128.5, 128.0, 127.1, 126.0; IR (cm^{-1}) 3334, 1494, 1448, 1016, 965, 741, 692; MS *m/z* 156 (100), 141 (30), 128 (48), 115 (54); HRMS calcd for $C_{12}H_{14}O$ 174.1045, obsd 174.1037.

Epoxide 10. Vanadyl acetylacetonate (57.2 mg, 0.22 mmol) was added to diene **9** (1.50 g, 8.61 mmol) in CH_2Cl_2 (12.6 mL) at −78 °C. After 30 min, *tert*-butyl hydroperoxide (5.8 mL of 3.74 M in CH_2Cl_2 21.6 mmol) was added dropwise over 10 min. After 24 h at rt, the mixture was partitioned between MTBE and, sequentially, 1 N aqueous NaOH and saturated brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give **10** (0.85 g, 4.47 mmol, 52%) as a pale yellow oil: TLC R_f (40% MTBE/petroleum ether) = 0.20; ^{1}H NMR δ 2.17 (bs, 1H), 2.36−2.64 (m, 2H), 3.15−3.26 (m, 2H), 3.76 (dd, J = 6.4 Hz, 12.2 Hz, 1H), 3.91 (dd, J = 4.0 Hz,12.2 Hz, 1H), 6.22 (dt, J = 15.9 Hz, 6.8 Hz, 1H), 6.51 (d, J = 15.9 Hz, 1H), 7.18−7.42 (m, 5H); ^{13}C NMR δ u 137.0, 60.7, 31.7; d 132.5, 128.5, 127.4, 126.1, 124.6, 56.7, 56.1; IR (cm^{-1}) 3408, 1449, 1039, 967; MS *m/z* 190 (58), 159 (31), 129 (82), 117 (100); HRMS calcd for $C_{12}H_{14}O_2$ 190.0994, obsd 190.1001.

Nitrile 11. To *n*-butyllithium (2.32 M in THF, 3.10 mL) in THF (8.60 mL) was added acetonitrile (0.41 mL, 7.76 mmol) dropwise over 10 min at −78 °C. After 1 h, the mixture was warmed to 0 °C, and the epoxide **10** (0.53 g, 2.87 mmol) in THF (3.40 mL) was added quickly. After 3 h, the mixture was partitioned between saturated aqueous NH_4Cl and MTBE. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was dissolved in 2,2-dimethoxypropane (8.78 mL, 71.40 mmol) and *p*-toluenesulfonic acid monohydrate (0.20 g, 1.05 mmol) was added. After 12 h at RT, the mixture was partitioned between aqueous $NaHCO_3$ and MTBE. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give **11** (0.53 g, 1.95 mmol, 71%) as a pale yellow oil: TLC R_f (20% MTBE/petroleum ether) = 0.32; ^{1}H NMR δ 1.40 (s, 3H), 1.45 (s, 3H), 1.76−1.82 (m, 1H), 2.16−2.28 (m, 1H), 2.36−2.56 (m, 3H), 2.82 (dd, J = 10.1 Hz, 16.9 Hz, 1H), 3.95 (d, J = 1.5 Hz, 1H), 4.06−4.16 (m, 2H), 6.11 (ddd, J = 6.1, 8.1, 15.8 Hz, 1H), 6.48 (d, J = 15.8 Hz, 1H), 7.19−7.37 (m, 5H); ^{13}C NMR δ u 136.9, 119.3, 99.3, 63.3, 36.1, 13.4; d 133.0, 128.5, 127.4, 126.0, 124.2, 70.3, 34.1, 29.5, 18.7; IR (cm^{-1}) 2244, 1382, 1198, 1163, 1081; MS *m/z* 256 (12), 155 (18), 154 (100); HRMS calcd for $C_{17}H_{21}NO_2$ 271.1572, obsd 271.1571.

Alcohol 12. The acetonide **11** (0.48 g, 1.77 mmol) was dissolved in CH_2Cl_2 (5.5 mL) and methanol (11.0 mL). Ozone was bubbled through for 30 min at −78°C. After excess ozone was purged with N_2, sodium borohydride (0.13 g, 3.55 mmol) was added. After 3 h at rt, the solvent was evaporated and the residue was partitioned between MTBE and, sequentially, saturated aqueous NH_4Cl and saturated brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give **12** (0.27 g, 1.36 mmol, 77%) as a pale yellow oil: TLC R_f (15% acetone/CH2Cl2) = 0.33; ^{1}H NMR δ 1.38 (s, 3H), 1.48 (s, 3H), 1.55−1.81 (m, 3H), 2.49−2.58 (m, 2H), 2.80 (dd, J = 9.8 Hz, 17.0 Hz, 1H), 3.71 (t, J = 5.0 Hz, 2H), 3.90 (dd, J = 1.5 Hz, 12.4 Hz, 1H), 4.14 (dd, J = 1.5 Hz, 12.4 Hz, 1H), 4.26−4.32 (m, 1H); ^{13}C NMR δ u 119.4, 99.2, 63.2, 59.4, 35.0, 13.6; d 68.8, 34.8, 29.4, 18.7; IR (cm^{-1}) 3470, 2245, 1383, 1198, 1078; MS *m/z* 184 (100), 110 (26), 94 (65); HRMS calcd for $C_{10}H_{17}NO_3$ ($M + H^+$) 200.1287, obsd 200.1287. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Obsd: C, 60.37; H, 8.65; N, 7.09.

Ether 13. Sodium hydride (60% in mineral oil, 82.0 mg, 2.06 mmol) was added to benzyl bromide (0.18 mL, 1.51 mmol) in THF (0.7 mL). After 5 min, alcohol **12** (0.27 g, 1.36 mmol) in THF (6.0 mL) was added dropwise over 10 min. After 24 h at rt, the mixture was partitioned between saturated aqueous NH_4Cl and MTBE. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give **13** (0.32 g, 1.11 mmol, 82%) as a pale yellow oil, TLC R_f (40% MTBE/petroleum ether) = 0.40; ^{1}H NMR δ 1.36 (s, 3H), 1.42 (s, 3H), 1.63−1.76 (m, 3H), 2.48 (dd, J = 4.7 Hz, 16.8 Hz , 1H), 2.76 (dd, J = 10.1 Hz, 16.8 Hz, 1H), 3.53 (t, J = 5.9 Hz, 2H), 3.90 (d, J = 12.3 Hz, 1H), 4.10 (d, J = 12.3 Hz, 1H), 4.25 (dt, J = 2.1, 6.6 Hz, 1H), 4.48 (d, J = 2.5 Hz, 2H), 7.26−7.39 (m, 5H); ^{13}C NMR δ u 138.1, 119.5, 99.3, 73.2, 65.8, 63.3, 33.1, 13.7; d 128.4, 127.7, 127.7, 67.4, 34.9, 29.6, 18.8; IR (cm^{-1}) 2244, 1382, 1198, 1084, 699; MS *m/z* 274 (100), 154 (34), 107 (29), 105 (96); HRMS for $C_{17}H_{23}NO_3$ calcd 289.1665, obsd 289.1668. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Obsd: C, 70.91; H, 8.02; N, 4.93.

Ester 14. A mixture of the nitrile **13** (2.13 g, 7.35 mmol), ethylene glycol (5.6 mL), water (9.3 mL), methanol (17.8 mL) and sodium hydroxide (2.73 g, 68.3 mmol) was heated and methanol was distilled off until the temperature of the mixture reached 110 °C. The mixture was then maintained at reflux (bath=110 °C) until no ammonia emission could be detected with moist pH paper. The mixture was cooled to rt, and DMF (54.3 mL) and methyl iodide (7.3 mL, 117.5 mmol) were added. After 12 h at RT, the mixture was partitioned between water and

(17) For the preparation and applications of rhodium triphenylacetate, see Hashimoto, S.-I.; Watanabe, N.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1508.

(18) For general experimental procedures, see Taber, D. F.; Meagley, R. P.; Doren, D. J. *J. Org. Chem.* **1996**, *61*, 5723.

MTBE. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give **14** (1.85 g, 5.74 mmol, 78%) as a pale yellow oil: TLC R_f (20% MTBE/petroleum ether) = 0.33; ^{1}H NMR δ 1.36 (s, 3H), 1.42 (s, 3H), 1.63−1.72 (m, 2H), 1.84−1.89 (m, 1H), 2.48 (dd, J = 4.1 Hz, 16.7 Hz, 1H), 2.73 (dd, J = 9.4 Hz, 16.7 Hz, 1H), 3.48−3.64 (m, 2H), 3.66 (s, 3H), 3.74 (dd, J = 1.0 Hz, 12.0 Hz, 1H), 4.03−4.08 (m, 1H), 4.19−4.25 (m, 1H), 4.48 (d, J = 3.2 Hz, 2H), 7.25−7.38 (m, 5H); ^{13}C NMR δ u 173.9, 138.3, 98.8, 73.0, 66.2, 64.3, 33.1, 29.4; d 128.3, 127.6, 127.5, 68.0, 51.5, 34.0, 29.6, 19.0; IR (cm^{-1}) 1738, 1382, 1197, 1169, 1090, 738, 699; MS *m*/*z* 323 (7), 266 (16), 265 (100), 235 (5), 157 (44); HRMS for $C_{18}H_{26}O_5$ calcd 323.1858, obsd 323.1867. Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Obsd: C, 67.26; H, 8.05.

Diazoester 5. To lithium bis(trimethylsilyl) amide (0.57 g, 3.41 mmol) in THF (3.5 mL) at −78 °C was added ester **14** (0.26 g, 0.81 mmol) in THF (1.9 mL) dropwise over 5 min. After 40 min, the mixture was warmed to −40 °C, and 2,2,2-trifluoroethyl trifluoroacetate (0.15 mL, 1.13 mmol) was added quickly. After 18 h at RT, the mixture was partitioned between saturated NH_4-Cl and MTBE. The combined organic extract was dried (Na_2-SO_4) and concentrated. The residue was dissolved in CH_2Cl_2 (2.5 mL) at 0 °C and DBU was added in the dark. After 10 min, *p*-nitrobenzenesulfonyl azide (0.48 g, 2.43 mmol) was added. After 36 h at RT, the mixture was partitioned between MTBE and 1N aqueous NaOH. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give **5** (0.22 g, 0.63 mmol, 78%) as a bright yellow oil: TLC R_f (20% MTBE/petroleum ether) = 0.30; ^{1}H NMR δ 1.31 (s, 3H), 1.46 (s, 3H), 1.74−1.82 (m, 2H), 2.35 (d, J = 1.2 Hz, 1H), 3.49−3.63 (m, 2H), 3.74 (s, 3H), 3.94 (dd, J = 1.4, 11.8 Hz, 1H), 4.27 (dd, J = 2.6, 11.8 Hz, 1H), 4.33−4.39 (m, 1H), 4.48 (d, J = 4.1 Hz, 2H), 7.25−7.38 (m, 5H); ^{13}C NMR δ u 138.3, 99.3, 73.0, 65.7, 65.3, 33.7; d 128.3, 127.6, 127.5, 68.3, 51.9, 33.2, 28.4, 18.6; IR (cm^{-1}) 2089, 1694, 1437, 1230, 1097, 743, 699; MS *m*/*z* 321 (25), 264 (16), 263 (100), 231 (6), 171 (6), 155 (23); HRMS for $C_{18}H_{24}N_2O_5$ calcd 349.1763, obsd 349.1782.

Cyclopentane 3 and 4. To diazoester **5** (83.8 mg, 0.24 mmol) in CH_2Cl_2 (1.5 mL) was added rhodium pivalate (1.4 mg, 0.002 mmol) in CH_2Cl_2 (1.5 mL) dropwise over 5 min. After 20 min at rt, the solvent was evaporated and the residue was chromatographed to give **3** (37.4 mg, 0.12 mmol, 49%) and **4** (32.1 mg, 0.10 mmol, 42%) as pale yellow oils. For **3**: TLC R_f (25% MTBE/petroleum ether) = 0.32; ^{1}H NMR δ 1.26 (s, 3H), 1.38 (s, 3H), 1.72−1.85 (m, 1H), 2.30 (dd, J = 6.8 Hz, 13.6 Hz, 1H), 2.48 (m, 1H), 2.92 (dd, J = 5.3, 11.1 Hz, 1H), 3.71 (s, 3H), 3.91 (d, J = 4.4 Hz, 2H), 4.34 (t, J = 4.3 Hz, 1H), 4.51 (dd, J = 11.8, 12.4 Hz, 2H), 4.81−4.89 (m, 1H), 7.25−7.37 (m, 5H); ^{13}C NMR δ u 173.4, 138.3, 98.1, 72.1, 58.2, 39.6, d 128.3, 127.7, 127.6, 81.6, 71.1, 51.8, 50.3, 40.2, 27.9, 20.1; IR (cm^{-1}) 1737, 1372, 1199, 1174, 1060, 738, 699; MS *m*/*z* 305 (20), 171 (20), 156 (100), 137 (40); HRMS for $C_{18}H_{24}O_5$ calcd 320.1624, obsd 320.1625.

For **4**: TLC R_f (25% MTBE/petroleum ether) = 0.27; ^{1}H NMR δ 1.30 (s, 3H), 1.36 (s, 3H), 1.89−2.00 (m, 1H), 2.66−2.35 (m, 1H), 2.64−2.78 (m, 1H), 2.95 (dd, J = 4.8, 9.0 Hz, 1H), 3.67 (s, 3H), 3.91−4.07 (m, 2H), 4.20 (dt, J = 3.5, 4.6 Hz, 1H), 4.37 (dt, J = 2.0, 7.2 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 4.63 (d, J = 11.9 Hz, 1H), 7.23−7.38 (m, 5H); ^{13}C NMR δ u 170.7, 138.6, 98.9, 70.8, 59.2, 36.8, d 128.1, 127.3, 127.3, 80.1, 70.4, 51.4, 51.0, 41.3, 26.0, 23.5; IR (cm^{-1}) 1740, 1379, 1222, 870, 737, 698; MS *m*/*z* 305 (54), 156 (100), 125 (30); HRMS for $C_{18}H_{24}O_5$ calcd 320.1624, obsd 320.1628.

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Supporting Information Available: ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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