Predicting the Diastereoselectivity of Rh-Mediated Intramolecular C−H Insertion

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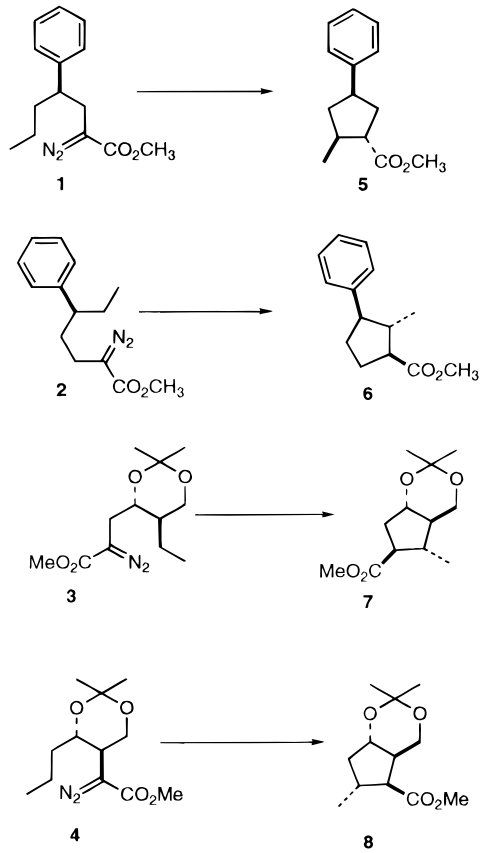
Abstract: Rhodium-mediated cyclization of the α-diazo ester **1** proceeds with high diastereoselectivity, to give the trisubstituted cyclopentane **5.** A computational model (ZINDO and Molecular Mechanics) based on our current mechanistic understanding of the reaction is presented. This model correctly predicts the dominant diastereomer from the cyclization of **1** and the eight (Table 2) other α-diazo esters studied thus far.

Introduction

The development of new methods for the stereocontrolled construction of carbocycles is fundamental to the development of target-directed organic synthesis. While many approaches for the preparation of enantiomerically-pure cyclopentanes have been put forward,[1] there is still a need for general strategies for the construction of highly-*alkylated* cyclopentanes with control of both relative and absolute configuration. As enantiomerically pure acyclic fragments of high enantiomeric purity are readily available, one way to fill this gap would be to develop methods for cyclization that proceed with high diastereoselectivity relative to existing stereogenic centers that are then included in the ring. We now report that the Rh-mediated cyclizations[2−5] of substituted α-diazo esters **1**, **2**, **3**, and **4** do indeed proceed with the desired high diastereoselectivity. We also present a computational model,[5−7] based on the cyclization of the α-diazo ester **1**, that accurately predicted the dominant diastereomer from the cyclization of the α-diazo esters **2**, **3**, **4**, and **42**.



Not all Rh-mediated intramolecular C−H insertion reactions will proceed to give a single dominant diastereomer. Our

[⊗] Abstract published in *Advance ACS Abstracts,* January 1, 1996.

(1) For leading references to alternative methods for the enantioselective construction of highly substituted cyclopentanes, see: (a) Allan, R. D.; Johnston, G. A. R.; Twitchin, B. *Aust. J. Chem.* **1979**, *32*, 2517. (b) Takahashi, T.; Naito, Y.; Tsuji, J. *J. Am. Chem. Soc.* **1981**, *103*, 5261. (c) Colombo, L.; Gennari, C.; Resnati, G.; Scolastico, C. *Synthesis*, **1981**, 74. (d) Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 4048. (e) Ziegler, F. E.; Mencel, J. J.; *Tetrahedron Lett.* **1983**, 1859. (f) Ritterskamp, P.; Demuth, M.; Schaffner, K. *J. Org. Chem.* **1984**, *49*, 1155. (g) Marino, J. P.; Fernandez de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1984**, 5280. (h) Block, E.; Wall, A.; Zubieta, J. *J. Am. Chem. Soc.* **1985**, *107*, 1783. (i) Binns, M. R.; Goodridge, R. J.; Haynes, R. K.; Ridley, D. D. *Tetrahedron Lett.* **1985**, 6381. (j) Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543. (k) Posner, G. H.; Switzer, C. *J. Am. Chem. Soc.* **1986**, *108*, 1239. (l) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1986**, *108*, 5655. (m) Stork, G.; Sher, P. M.; Chen, H. L. *J. Am. Chem. Soc.* **1986**, *108*, 6384. (n) Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7116. (o) Meyers, A. I.; Lefker, B. A. *J. Org. Chem.* **1986**, *51*, 1541. (p) Hua, D. H.; Venkataraman, S.; Coulter, M. J.; Sinai-Zingde, G. *J. Org. Chem.* **1987**, *52*, 719. (q) Burgess, K. *J. Org. Chem.* **1987**, *52*, 2046. (r) Klunder, A. J. H.; Huizinga, W. B.; Sessnik, P. J. M.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*, 357. (s) Smith, A. B., III; Dunlap, N. K.; Sulikowski, G. A. *Tetrahedron Lett.* **1988**, 439. (t) Trigalo, F.; Buisson, D.; Azerad, R. *Tetrahedron Lett.* **1988**, *29*, 6109. (u) Llera, J. M.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 5544. (v) Snider, B. B.; Ke, Y. *Tetrahedron Lett.* **1989**, *30*, 2465. (w) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1990**, *112*, 9601. (x) Stafford, J. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 5433. (y) Brown, R. T.; Ford, M. J. *Tetrahedron Lett.* **1990**, 2029. (z) Asaoka, M.; Hayashibe, S.; Sonoda, S.; Takei, H. *Tetrahedron Lett.* **1990**, *31*, 4761. (aa) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089. (bb) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378. (cc) Taber, D. F.; Silverberg, L. J.; Robinson, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6639. (dd) Chadha, N. K.; Batcho, A. D.; Tang, P. C.; Courtney, L. F.; Cook, C. M.; Wovkulich, P. M.; Uskokovic, M. R. *J. Org. Chem.* **1991**, *56*, 4714. (ee) Fang, C. L.; Suemune, H.; Sakai, K. *J. Org. Chem.* **1992**, *57*, 4300. (ff) Quinkert, G.; Muller, T.; Koniger, A.; Schultheis, O.; Sickenberger, B.; Durner, G. *Tetrahedron Lett.* **1992**, *33*, 3469. (gg) Kigoshi, H.; Imamura, Y.; Mizuta, K.; Niwa, H.; Yamada, K. *J. Am. Chem. Soc.* **1993,** *115*, 3056. (hh) Hanessian, S.; Gomtsyan, A.; Payne, A.; Herve, Y.; Beaudoin, S. *J. Org.Chem.* **1993**, *58*, 5032. (ii) Henly, R.; Elie, C. J. J.; Buser, H. P.; Ramos, G.; Moser, H. E. *Tetrahedron Lett.* **1993**, *34*, 2923. (jj) Doyle, M. P.; Dyatkin, A. B.; Roos, G. H. P.; Canas, F.; Pierson, D. A.; van Basten, A. *J. Am. Chem. Soc.* **1994**, *116*, 4507. (kk) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571. (ll) Koch, A.; Reymond, J. L.; Lerner, R. A. *J. Am. Chem. Soc.* **1994,** *116*, 803. (mm) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089. (nn) Mashima, K.; Kusano, K.; Sato, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064. (oo) Berl, V.; Helmchen, G.; Preston, S. *Tetrahedron Lett.* **1994**, *35*, 233. (pp) Zhu, J.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1994**, *35*, 2787.

(2) For a detailed account of regioselectivity and diastereoselectivity in the Rh-mediated cyclization of α-diazo *β*-keto esters, see: Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686.

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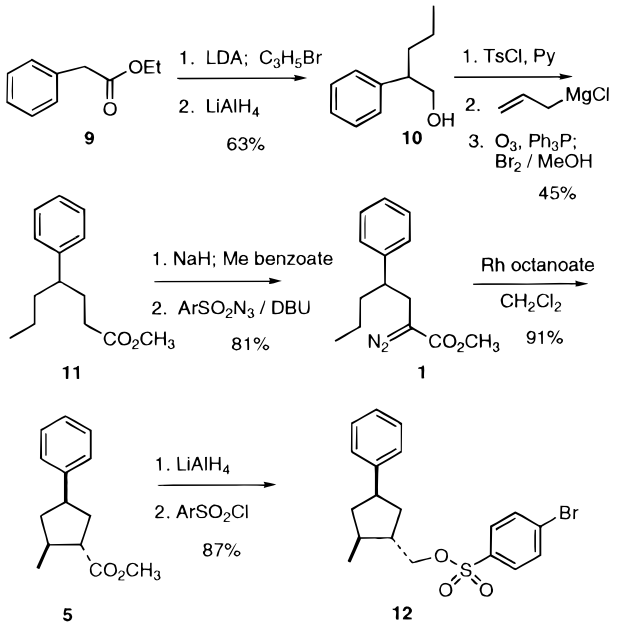
Scheme 1

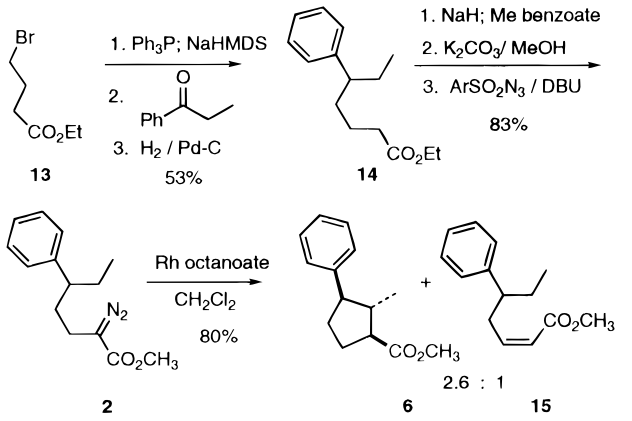


interest in this initial investigation has been to develop a model for the transition state that will allow us to discern those cyclizations that *will* proceed with high diastereoselectivity.

Results

Preparation and Cyclization of α-Diazo Ester 1. The requisite ester **11** (Scheme 1) was prepared by alkylation of ethyl phenylacetate **9** with 1-bromopropane. Coupling of the tosylate of the derived alcohol **10** with allyl magnesium chloride proceeded smoothly, to give the alkene. Ozonolysis followed by oxidation[8] then gave **11**. We found that this homologation sequence was more rapid and efficient than alternatives based on malonate or acetate anion alkylation.

Scheme 2



With **11** in hand, we needed to effect α-diazo transfer.[9] Formylation of **11** followed by diazo transfer was not successful. However, we found that diazo transfer could be accomplished by first benzoylating[10] the ester enolate, then cleaving the benzoyl group with DBU[11] and 4-nitrobenzenesulfonylazide[12] to afford **1**.

Cyclization of **1** proceeded smoothly to give **5** as a single diastereomer (>95% pure by ^{13}C NMR). As the ^{1}H NMR of **5** was ambiguous, the relative configuration of **5** was established by X-ray analysis of the derived 4-bromobenzenesulfonate **12**.

Preparation and Cyclization of α-Diazo Ester 2. To prepare **2**, we started with the bromo ester **13** (Scheme 2). Condensation of the derived phosphorane with propiophenone followed by hydrogenation gave ester **14**. Benzoylation by the procedure described above gave a mixture of methyl and ethyl esters, which was then fully exchanged to the methyl ester before diazo transfer. Cyclization of **2** proceeded to give **6** as the dominant diastereomer observed (>95% pure by ^{13}C NMR).

The relative configuration of **6** was assigned on the basis of ^{1}H and ^{13}C chemical shifts. Thus, the phenyl and the methyl must be trans, as the methyl resonates at δ 0.95. If the methyl and the phenyl were cis one to another, the methyl group would be expected to be shifted significantly upfield.[13]

The relationship between the methyl group and the ester was also assigned to be trans on the basis of the ^{13}C chemical shift of the methine carbon bearing the ester. The known[3,14] trans and cis 2-octyl cyclopentanecarboxylates have methine carbons at δ 50.4 and 46.5, respectively. That the ester-bearing methine in **6** resonates at δ 51.6 supports the trans assignment.

Preparation and Cyclization of α-Diazo Ester 3. The preparation of **3** started with the enantiomerically pure β-hydroxy ester **16** (Scheme 3), which we had prepared previously.[1cc] Ethylation following the procedure of Frater[15] gave the anti ester,

(3) (a) For the first observation of the efficient cyclization of simple α-diazo esters, see: Taber, D. F.; Hennessy, M. J.; Louey, J. P. *J. Org. Chem.* **1992**, *57*, 436. (b) For the first report of the cyclization of (enantiomerically pure) **3** to **7**, in the context of a total synthesis of the Dendrobatid alkaloid **251F**, see: Taber, D. F.; You, K. K. *J. Am. Chem. Soc.* **1995**, *117*, 5757.

(4) For leading references to other studies of Rh-mediated intramolecular C−H insertion, see: (a) Doyle, M. P.; Dyatkin, A. B.; Roos, G. H. P.; Canas, F.; Pierson, D. A.; van Basten, A.; Müller, P.; Polleux, P. *J. Am. Chem. Soc.* **1994**, *116*, 4507. (b) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296. (c) Doyle, M. P. In *Homogeneous Transition Metal Catalysts in Organic Synthesis*; Moser, W. R., Slocum, D. W., Eds.; ACS Advanced Chemistry Series 230; American Chemical Society: Washington, D.C., 1992; Chapter 30. (d) Taber, D. F. *Comprehensive Organic Synthesis*; Pattenden, G., Ed., Pergamon Press: Oxford, 1991; Vol. 3, p 1045. (e) Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797.

(5) For related analyses of transition states for Rh carbene insertions, see: (a) Doyle, M. P.; Westrum, L. J.; Wolthius, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958. (b) Brown, K. C.; Kodadek, T. *J. Am. Chem. Soc.* **1992**, *114*, 8336. (c) Pirrung, M. C.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 8991. (d) Davies, H. M. L.; Huby, N. J. S.; Cantrell, W. R., Jr.; Olive, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 9468.

(6) Both ZINDO and molecular mechanics were used as implemented on the Tektronix CAChe workstation. For leading references to ZINDO, a semiempirical program that has been paramatrized for the first two rows of transition metals, see: (a) Zerner, M. C.; Loew, G. W.; Kirchner, R. F.; Mueller-Westerhoff, U. T. *J. Am. Chem. Soc.* **1980**, *102*, 589. (b) Anderson, W. P.; Cundari, T. R.; Drago, R. S.; Zerner, M. C. *Inorg. Chem.* **1990**, *29*, 1.

(7) For an analogous experimental/computational study of intramolecular diene cyclozirconation, see: Taber, D. F.; Louey, J. P.; Wang, Y.; Nugent, W. A.; Dixon, D. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1994**, *116*, 9457.

(8) Williams, D. R.; Klingler, F. D.; Allen, E. E.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1988**, *29*, 5087.

(9) For an overview of diazo transfer chemistry, see: (a) Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: Orlando, 1986. (b) Askani, R.; Taber, D. F. *Comprehensive Organic Synthesis;* E. Winterfeldt, Ed., Pergamon: Oxford, 1991; Vol. 6, p 103.

(10) (a) For benzoylation of a *ketone* followed by diazo transfer, see: Metcalf, B. W.; Jund, K.; Burkhart, J. P. *Tetrahedron Lett.* **1980**, *21*, 15. (b) More recently, trifluoroacetylation has been used to activate ketones for diazo transfer: Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.

(11) For the use of DBU to promote diazo transfer, see: (a)Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709. (b) Koteswar Rao, Y.; Nagarajan, M. *J. Org. Chem.* **1989**, *54*, 5678.

(12) (a) Evans, seeking azide transfer, reported occasional partial conversion of an ester enolate to the α-diazo ester: Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011. (b) We have optimized this procedure: Taber, D. F.; You, K.; Song, Y. *J. Org. Chem.* **1995**, *60*, 1093.

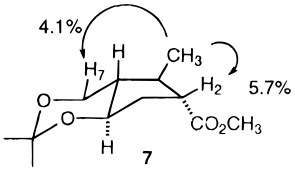
(13) Taber, D. F.; Meagley, R. P. *Tetrahedron Lett.* **1994**, *35*, 7909.

(14) Louey, James P. Ph.D. Dissertation, University of Delaware, 1994.

(15) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825.

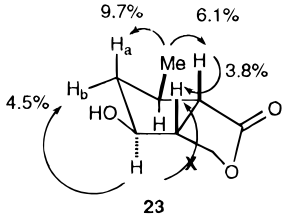
which on reduction and protection gave the acetonide **17**. Oxidative cleavage, as above, followed by diazo transfer then gave **3**.

Cyclization of **3** proceeded cleanly, to give **7** as the only diastereomer observed (>95% pure by ^{13}C NMR before chromatographic separation). The relative configuration of **7**



was assigned by a combination of COSY and NOE techniques. The most significant observations were a 4.1% NOE between the methyl group and the equatorial H at C-7 and a 5.7% NOE between the methyl group and the H at C-2. The lack of an NOE between the ring fusion H's confirmed the trans ring fusion. Given the rigid nature of the chair conformation of the six-membered ring, these observations then secure the relative configuration of **7**. This facile preparation of a polyalkylated cyclopentane with control of relative and (through the use of the readily available enantiomerically pure starting material) absolute configuration underscores the likely utility of this approach in target-directed synthesis.

Preparation and Cyclization of α-Diazo Ester 4. We prepared the complementary α-diazo ester **4** (Scheme 4) from butyraldehyde **19** by aldol condensation followed again by Frater[15] alkylation. It is noteworthy that in this case the cyclization proceeded to give **8** (>95% pure by ^{13}C NMR), which is *not* the most stable diastereomer of the product. That the single dominant diastereomer from the cyclization was in fact **8** was confirmed by deprotection with spontaneous lactonization to give **23**.

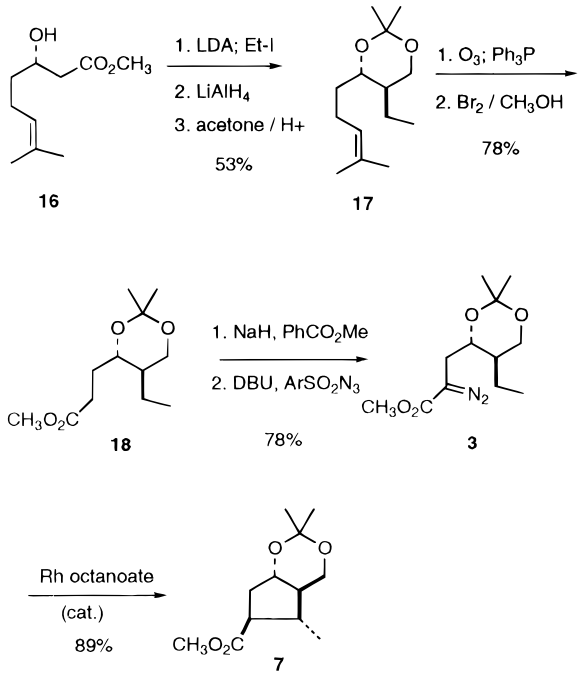


NOE studies supported our assignment of structure **23** to the product from deprotection of acetonide **8**. The cis nature of the ring fusion was demonstrated by a 3.8% NOE between the two ring fusion hydrogens. An NOE of 6.1% between the ring fusion hydrogen α to the carbonyl and the adjacent methyl group confirms that the methyl group is exo on the bicyclic system. The diastereotopic protons of the single methylene could be distinguished. One showed a 9.7% NOE to the methyl group, and the *other* showed a 4.5% NOE to the proton a to the hydroxyl group. Finally, that same proton α to the hydroxyl group did *not* show an NOE with the ring fusion methine.

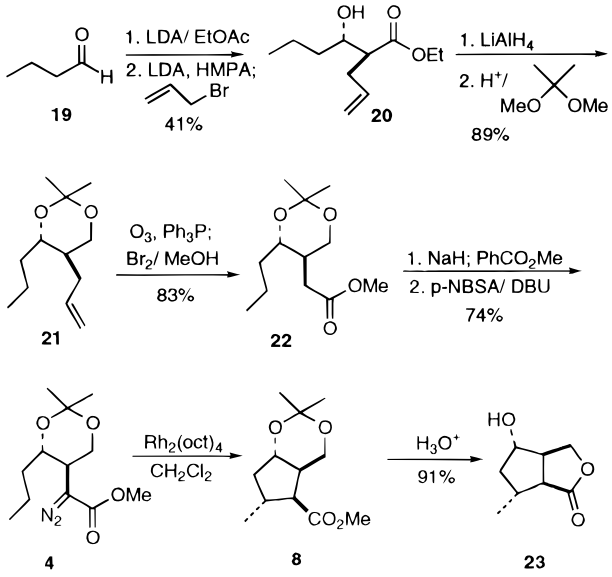
Discussion

Mechanism of the Cyclization. An understanding of the mechanism[4,5] for Rh-mediated intramolecular C−H insertion begins with the recognition that these α-diazo carbonyl derivatives can also be seen as the stabilized ylides, such as **24** (Scheme 5). The catalytic Rh(II) carboxylate **25** is Lewis acidic, with vacant coordination sites at the apical positions. Complexation of the electron density at the diazo carbon with an open Rh coordination site would give **26**. Back donation of electron density from the proximal Rh to the carbene carbon[5c]

Scheme 3



Scheme 4

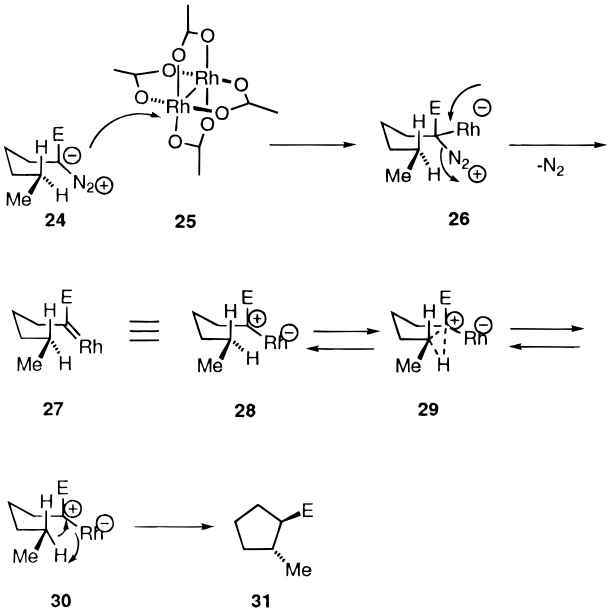


with concomitant loss of N_2 would then give the intermediate Rh carbene complex **27**.

The mechanism by which this intermediate Rh carbene complex **27** reacts can be more easily understood if it is written as the inverted ylide **28**. This species would clearly be electrophilic at carbon. The initial complex of the electron-deficient carbon with the electron density in the target C−H could be depicted (**29**) as a three-center, two-electron bond.[5a] We hypothesized that this complexation would be rapid and reversible,[16] and that for bond formation to proceed, *a somewhat different transition state (**30**)*, in which the C−Rh bond is aligned with the target C−H bond, would be required. As the C−H insertion reaction proceeded, the electron pair in the C−H bond would drop down to form the new C−C bond, and at the same time the electron pair in the C−Rh bond would slide over

(16) For reversible Rh complexation with a C−H bond, see: (a) Weiller, B. H.; Wasserman, E. P.; Bergman, R. G.; Moore, C. B.; Pimentel, G. C. *J. Am. Chem. Soc.* **1989**, *111*, 8288. (b) Wasserman, E. P.; Moore, C. B.; Bergman, R. G. *Science* **1992**, *255*, 315.

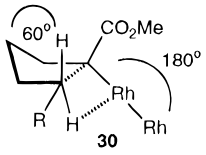
Scheme 5



to form the new C−H bond. This would give the product (**31**) and release the initial Rh species **25**, completing the catalytic cycle. We have used this hypothetical transition state (**30**) to predict the stereochemical course of the intramolecular Rh-mediated C−H insertion reaction and have found it to be effectively predictive.

The actual product from a cyclization will be determined as the intermediate carbene *commits* to a particular diastereomeric transition state. If these diastereomeric transition states are indeed in full thermal equilibrium, then computational modeling of the diastereomeric transition states (**30**) could allow us to predict which would be favored, and thus which diastereomeric product would be formed.

Development of the Computational Model. To construct the transition state **30**,[6,7] we minimized $Rh_2(OAc)_4$[17] with ZINDO and locked the resultant bond lengths and bond angles. To maintain the expected carbene geometry, we locked the Rh−Rh−C bond angle at 180°. To secure overlap between the C−Rh bond and the target C−H bond, we established weak bonds (meaningful in molecular mechanics) between the two incipiently bonding carbons and between the target H and the proximal Rh. As Mechanics tends to rehybridize weakly bonded carbons, we also found it necessary to lock the H−C−C−C dihedral angle of the target C−H at 60° (or, in the inverted transition state, −60°), to maintain sp^3 geometry.



There are still two possibilities for the transition state, illustrated (Chart 1) for the rhodium carbene derived from the α-diazo ester **1**. In transition state **33**, the Rh carbene is pointed away from the flip of the incipient cyclopentane ring (a "chair-like" transition state, counting the five carbons and the Rh in the six-membered ring), whereas in **34** the Rh carbene is pointed toward the flip of the incipient cyclopentane ring (a "boat-like" transition state). As **1** (Scheme 1) cyclizes to **5**, in which the methyl and the phenyl are on the same face of the cyclopentane, we concluded that at the point of commitment to product formation, the transition state leading to cyclization is chair-like (**33**, Chart 1) rather than boat-like (**34**).

Application of the Computational Model

Cyclization of α-Diazo Esters. There are four chair-like diastereomeric transition states for the cyclization of **1**, **35**, **36**, **38**, and **40** (Table 1), each leading to one of the four possible diastereomeric products. With the Rh catalyst locked and the angles and bonds as stated, we minimized each of the four transition states with molecular mechanics.[6] Transition state **35** was found to be the lowest in energy, by 5.3 kcal/mol compared to the next most stable. This contrasts with the relative stability of the four diastereomeric *products*, **5**, **37**, **39**, and **41** (Table 1), which are quite comparable one to another.

For each of the other α-diazo esters (Table 2), this computational approach reliably predicted the dominant diastereomer from the cyclization. It is noteworthy that in the case of **4**, the computational method predicted that **8**, not the most stable diastereomer of the product, should be the one produced. This was, in fact, observed (Scheme 4).

Cyclization of α-Diazo *β*-Keto Esters. We had previously reported[2] diastereoselectivity in the cyclization of α-diazo *β*-keto esters. These results are summarized in Table 2, Entries 5−8. We have found that the computational approach outlined above can be extended to these systems also. Entries 6−8 delineate the lower limit of this computational approach: when the two most favorable diastereomeric transition states are found to differ by less than 2.0 kcal/mol, the cyclization may not proceed with high diastereoselectivity.

Again, for this computational approach to be at all meaningful, it is requisite that the four diastereomeric transition states (**30**, Scheme 5) be fully equilibrating, that is, that the complexation of the Rh carbene with the target C−H must be rapidly reversible.[16] The correlation between the computational and experimental results presented here does not conclusively demonstrate such equilibration. It remains to be seen as we extend this approach to other substituted α-diazo esters whether the correlation is maintained.

Electron-Withdrawing Effects of Remote Substituents. The observance of alkene **15** from the cyclization of **2** underlines a key consideration that governs the use of Rh-mediated intramolecular C−H insertion in target-directed synthesis. We[2] and others[4,19] have observed that a proximal electron-withdrawing group will attenuate the reactivity of a target C−H bond. In **1**, the electron-withdrawing phenyl group inhibits *β*-hydride elimination, and the cyclization proceeds efficiently. In **2**, the electron-withdrawing phenyl group inhibits intramolecular C−H insertion, and the (no longer inhibited) *β*-hydride elimination proceeds at a competitive rate.

The cyclization of **4** is the first example of Rh-mediated intramolecular C−H insertion of an α-diazo ester having a *β*-ternary center. The methine C−H of the ternary center is much more electron rich, and so much more susceptible to elimination,[3] than the C−H of a methylene. In the case of **4**, there are, by design, two electron-withdrawing ether oxygens *γ* to the carbonyl and thus *β* to the C−H, making it less electron rich and thus less likely to eliminate.[20]

(17) We used $Rh(II)_2(acetate)_4$ in the model, and $Rh(II)_2(octanoate)_4$ in the cyclizations. While the computational predictions are consistent with the experimental obervations (Tables 1 and 2), we[2] and others[18] have shown that ligand substitution can affect the diastereoselectivity of Rh-mediated intramolecular C−H insertion.

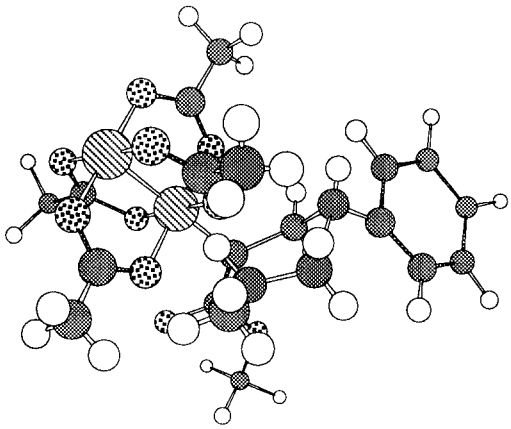
(18) Hashimoto, S.-i.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 2709.

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

(20) Note that while an H *β* to an ether is deactivated for Rh-mediated insertion, the α-H of an ether is activated.[4b]

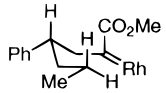
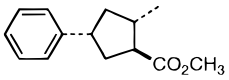
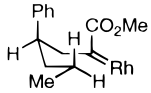
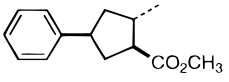
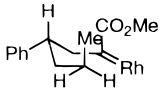
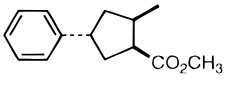
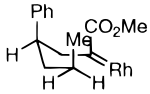
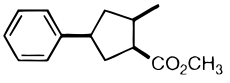
Chart 1

33



34

Table 1. Calculated Relative Energies of Transition States and Products

entry	possible diastereomeric T.S.	possible diastereomers	relative T.S. stabilities (ΔE), Kcalmol^{-1}	relative product stabilities (ΔE), Kcalmol^{-1}
1	 **35**	 **5**	0.0	0.0
2	 **36**	 **37**	5.3	0.1
3	 **38**	 **39**	6.1	0.2
4	 **40**	 **41**	7.4	0.9

Conclusion

The creation of new methods for the enantioselective construction of carbocycles is fundamental to the development of target-directed organic synthesis. The computational approach outlined here should allow the design of other α-diazo esters that will also cyclize with high diastereoselectivity. This approach will be complementary to the elegant enantioselective C−H insertions developed by Doyle[3a] and Ikegami,[21] allowing the direct construction of more highly-substituted cyclopentanes with control of relative and absolute configuration. Diastereoselective Rh-mediated cyclization of a substituted α-diazo ester, guided by the combined computational and experimental approach outlined here, should become a useful tool in the armamentarium of the organic synthesis chemist. Nevertheless, the work outlined here is only a bare beginning. While it appears to be possible, with this approach, to pick out those α-diazo esters that will cyclize with high diastereoselectivity, the method put forward is not sufficient to distinguish small differences in energy between closely competing transition states. We eagerly await the more precise computational methods that might effectively address these small differences.

Experimental Section[22]

Calculations. Structure minimization was carried out using molecular mechanics and ZINDO programs provided in the Tektronics CAChe System, Version 2.8. CAChe uses an augmented version of Allinger's MM2 force field.

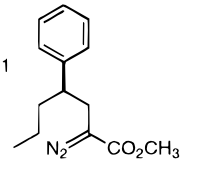
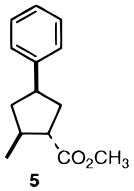
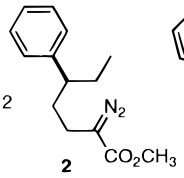
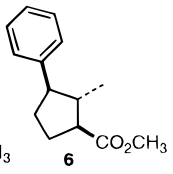
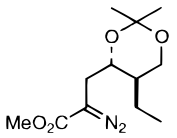
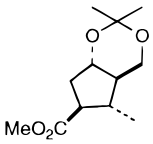
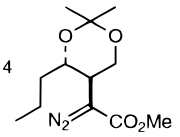
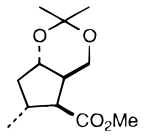
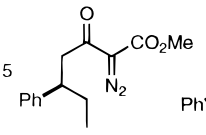
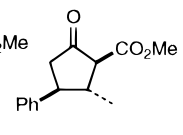
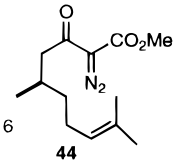
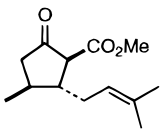
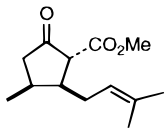
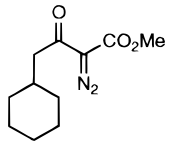
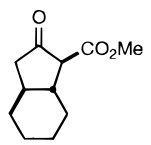
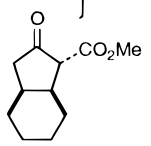
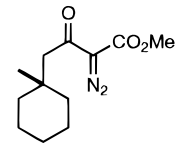
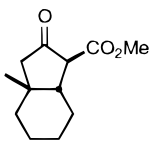
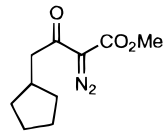
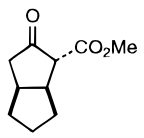
2-Phenylpentan-1-ol (10). *n*-Butyllithium (26.6 mL, 63.3 mmol, 2.38 M in hexane) was added to a stirring solution of diisopropylamine (9.5 mL, 68.21 mmol) in THF (120 mL) at −78 °C. After 10 min, ethyl phenylacetate (**9**); (8.0 g, 48.7 mmol) and 1-bromopropane (7.19 g, 58.5 mmol) were added sequentially to the reaction mixture. The mixture was stirred with warming to room temperature over 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (100 mL) and diluted with ethyl ether (70 mL). The organic layer was separated and the aqueous layer was extracted with 1:3 ethyl acetate/petroleum ether (3 × 60 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to yield the alkylated ester (7.08 g) as a pale yellow oil, TLC $R_f = 0.71$ (10% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 7.43−7.20 (m, 5 H), 4.18−3.99 (m, 2 H), 3.56 (t, $J = 7.3$ Hz, 1 H), 2.01 (m, 1 H), 1.77 (m, 1 H), 1.31 (m, 2 H), 1.27 (t, $J = 7.1$ Hz, 3 H), 0.93 (t, $J = 7.2$ Hz, 3 H). ^{13}C NMR (δ): d: 13.79, 14.11, 51.53, 127.0, 127.9, 128.5; u 20.72, 35.69, 60.57, 139.4, 174.1. IR (cm^{-1}): 3027, 2930, 2872, 1738, 1603, 1494, 1453, 1164. MS (*m*/*z*, %): 206 (M^+, 15), 164 (100), 133 (79), 104 (43). HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1266.

Lithium aluminum hydride (2.22 g, 58.5 mmol) was added to a solution of the alkylated ethyl ester (6.50 g, 31.5 mmol) in THF (100 mL). The reaction mixture was heated to reflux for 10 h, then cooled to 0 °C. H_2O (3 mL), aqueous 10% NaOH (3 mL), and H_2O (9 mL) were added sequentially to the grayish reaction mixture over a period of 2 h. Substantial gas and heat evolution were observed, and the reaction mixture turned into a white suspension. This suspension was filtered and the residue was rinsed with three portions of ethyl acetate (90 mL). The combined filtrate was concentrated and chromatographed to give the alcohol **10** (4.50 g, 63% yield from **9**) as a colorless oil, TLC $R_f = 0.51$ (20% ethyl acetate/petroleum ether). ^{1}H NMR (δ):

(21) (a) Hashimoto, S.-i.; Watanabe, N.; Sato, T.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1993**, *33*, 5109. (b) Hashimoto, S.-i.; Watanabe, N.; Kawano, K.; Ikegami, S. *Synth. Commun.* **1994**,24, 3277.

(22) For a general experimental procedure, see: Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1994**, *59*, 4004.

Table 2. Calculated T.S. Energy Differences and Diastereomeric Ratios

entry	starting material	Product(s)	relative T.S. stabilities (ΔE), Kcalmol^{-1}	yield,%
1	 **1**	 **5**	5.3	91[a]
2	 **2**	 **6**	2.5	62[a]
3	 **3**	 **7**	3.8	89[a]
4	 **4**	 **8**	4.7	85[a]
5	 **42**	 **43**	2.6	77[b]
6	 **44**	 **45** +  **46** (2 : 1)	1.7	82[b]
7	 **47**	 **48** +  **49** (3 : 1)	1.8	63[b]
8	 **50**	 **51**	1.7	93[b]
9	 **52**	 **53**	2.5	45[b]

[a] Cyclization was carried out using rhodium octanoate. [b] Cyclization was carried out using rhodium acetate.

7.38−7.20 (m, 5 H), 3.75 (m, 2 H), 2.77 (m, 1 H), 1.61 (m, 2 H), 1.36 (s br, 1 H), 1.23 (m, 2 H), 0.88 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (δ): d 14.2, 48.5, 126.7, 128.1, 128.7; u 20.5, 34.3, 67.7, 142.6. IR (cm^{-1}): 3346, 2930, 2871, 1602, 1493, 1453, 1379. MS (*m*/*z*, %): 164 (M$^+$, 26), 147 (36), 133 (100), 115 (21), 103 (67). HRMS calcd for $C_{11}H_{16}O$ 164.1202, found 164.1210.

Methyl 3-Phenylheptanoate (11). *p*-Toluenesulfonyl chloride (4.88 g, 25.6 mmol) was added to a mixture of alcohol **10** (3.50 g, 21.3 mmol) in pyridine (10 mL) and CH_2Cl_2 (30 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h, then partitioned between CH_2Cl_2 and 10% aqueous HCl. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the tosylate (6.04 g) as a white powder, TLC R_f = 0.58 (20% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 7.63 (d, J = 8.4 Hz, 2 H), 7.21 (m, 5 H), 7.11 (m, 2 H), 4.18 (m, 2 H), 2.89 (m, 1 H), 2.41 (s, 3 H), 1.73 (m, 1 H), 1.57 (m, 1 H), 1.18 (m, 2 H), 0.82 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (δ): d: 13.87, 21.59, 44.82, 126.9, 127.8, 128.5, 129.7; u 20.09, 33.87, 73.97, 132.5, 140.5, 144.5.

Allylmagnesium chloride (35 mL, 69.1 mmol, 2.0 M in THF) was added to an ice-cold solution of the tosylate (11.0 g, 34.57 mmol) in THF (115 mL). After stirring with warming to room temperature for 13 h, saturated aqueous NH_4Cl (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with 1:4 ethyl acetate/petroleum ether (3 × 40 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the coupled product (4.74 g) as a colorless oil, TLC R_f = 0.76 (10% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 7.22 (m, 5 H), 5.72 (m, 1 H), 4.91 (m, 2 H), 2.53 (m, 1 H), 1.88 (q, J = 7.2, 1 H), 1.60 (m, 4 H), 1.15 (m, 2 H), 0.86 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (δ): d 14.12, 45.13, 125.8, 127.7, 128.2, 138.9; u 20.67, 31.75, 36.03, 39.16, 114.3, 145.8. MS (*m*/*z*, %): 188 (M$^+$, 21), 146 (89), 133 (67), 118 (100). HRMS calcd for $C_{14}H_{20}$ 188.1566, found 188.1571.

A stream of ozone was passed through a solution of the above alkene (2.47 g, 13.1 mmol) in CH_2Cl_2 (130 mL) at −70 °C until the red indicator (Sudan Red) was decolorized (11 min). The ozone was turned off and the reaction mixture was flushed with N_2. Triphenylphosphine (4.1 g, 15.8 mmol) was added, and the reaction mixture was allowed to warm to room temperature over 13 h. The reaction mixture was concentrated and the residue was diluted with 9:1 CH_3OH/H_2O (33 mL). $NaHCO_3$ (11.0 g, 0.13 mol) and a solution of bromine (30 mL, 1.95 M in 9:1 CH_3OH/H_2O) were added sequentially to the reaction mixture. The mixture turned bright orange, with gas evolution. After

10 min of stirring, $Na_2S_2O_3 \cdot 5H_2O$ (25.0 g, 0.10 mol) was added to the reaction mixture. The mixture was instantly decolorized, with additional gas evolution. The mixture was diluted with H_2O (20 mL) and ether (20 mL). The organic phase was separated, and the aqueous phase was extracted with ether (3 × 40 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the desired ester **11** (1.98 g, 45% yield from **10**) as a pale yellow oil, TLC $R_f = 0.56$ (10% ethyl acetate/petroleum ether). ^{1}NMR (δ): 7.41−7.0 (m, 5 H), 3.61 (s, 3 H), 2.48 (m, 1 H), 2.18−1.80 (m, 4 H), 1.58 (m, 2 H), 1.17 (m, 2 H), 0.86 (t, $J = 7.2$ Hz, 3 H). ^{13}C NMR (δ): d 14.0, 45.2, 51.3, 126.1, 127.6, 128.3; u 20.6, 31.7, 32.2, 40.0, 144.6, 174.1. IR (cm^{-1}): 3027, 2931, 2872, 1738, 1603, 1494, 1453, 1377, 1202; MS (*m*/*z*, %): 220 (M^+, 28), 188 (44), 146 (42), 133 (31), 117 (100). HRMS calcd for $C_{14}H_{20}O_2$ 220.1464, found 220.1469.

Methyl 2-Diazo-4-phenylheptanoate (1). Sodium hydride (0.8 g, 27.0 mmol, 80% in mineral oil), methyl benzoate (2.2 mL, 18.0 mmol), and 2 drops of CH_3OH were added sequentially to an ice-cold solution of ester **11** (1.98 g, 9.0 mmol) in DME (40 mL). The reaction mixture was heated to reflux for 13 h, then was chilled to room temperature. Aqueous acetate buffer (10 mL, 0.25 M, pH = 5) was added to the reaction mixture, followed by ether (10 mL). The resultant mixture was extracted with 30% ethyl acetate/petroleum ether (3 × 30 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the diastereomeric benzoyl esters (2.77 g) as a pale yellow oil, TLC $R_f = 0.41$ (10% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 7.79−7.0 (m, 10 H), 4.16 (m, 1 H), 3.78, 3.83 (2s, total 3 H), 2.48 (m, 2 H), 2.11 (m, 2 H), 1.61 (m, 2 H), 1.18 (m, 2 H), 0.82 (m, 3 H). ^{13}C NMR (δ): d 14.0, 43.4, 44.0, 51.2, 52.1, 52.4, 52.5, 126.1, 126.4, 127.7, 127.9, 128.5, 128.6, 128.7, 133.4; u 20.5, 20.6, 35.8, 36.2, 39.1, 39.4, 135.3, 136.6, 143.9, 144.0, 170.3, 170.5, 195.5, 195.6.

1,8-Diazabicyclo[5.4.0]undec-7-ene (1.6 mL, 10.5 mmol) and 4-nitrobenzenesulfonyl azide (2.4 g, 10.5 mmol in 5 mL CH_2Cl_2) were added to an ice-cold solution of the benzoyl ester (1.86 g, 5.2 mmol) in CH_2Cl_2 (20 mL). After warming to room temperature (1 h), aqueous phosphate buffer (8 mL, 0.5 M, pH = 7) was added to the reaction mixture. After stirring for an additional 30 min, the reaction mixture was partitioned between CH_2Cl_2 and brine. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give **1** (1.20 g, 81% yield from **11**) as a bright yellow oil, TLC $R_f = 0.55$ (10% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 7.35−7.09 (m, 5 H), 3.67 (s, 3 H), 2.80 (m, 1 H), 2.62 (dd, $J = 5.8$, 14.7 Hz, 1 H), 2.48 (dd, $J = 9.2$, 14.7 Hz, 1 H), 1.65 (m, 2 H), 1.24 (m, 2 H), 0.86 (t, $J = 7.2$ Hz, 3 H). ^{13} C NMR (δ): d 14.0, 44.7, 51.8, 126.6, 127.6, 128.5; u 20.5, 30.9, 37.7, 143.7, 168.0; IR (cm^{-1}): 2931, 2083, 1692, 1603, 1441, 1335, 1128, 701. MS (*m*/*z*, %): 187 (11), 171 (5), 157 (3), 131 (3), 128 (8), 120 (23), 119 (100), 116 (12), 104 (3), 100(45); HRMS calcd for $C_{14}H_{18}O_2N_2$ 246.1369 (218.1307 loss of N_2), found 218.1311.

Methyl (1*R,2*R**,4*S**)-2-Methyl-4-phenylcyclopanecarboxylate (5).** CH_2Cl_2 (25 mL) was passed through a pad of K_2CO_3 into the diazo compound **1** (1.2 g, 4.9 mmol). A catalytic amount of rhodium octanoate (2 mg, 0.0026 mmol) was added to the reaction mixture. The bright yellow reaction mixture was instantly decolorized with the evolution of gas. After the gas evolution had ceased (10 min), the reaction mixture was concentrated in vacuo. The dark green residue was chromatographed, eluting with 2% ethyl acetate/petroleum ether, to give a single diastereomer **5** (0.97 g, 91% yield) as a colorless oil, TLC $R_f = 0.58$ (5% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 7.35−7.09 (m, 5 H), 3.61 (s, 3 H), 3.19 (m, 1 H), 2.35−2.20 (m, 4 H), 1.98 (m, 1 H), 1.31 (q, $J = 11.1$ Hz, 1 H), 1.10 (d, $J = 6.3$ Hz, 3 H). ^{13} C NMR (δ): d 19.6, 39.8, 44.6, 51.0, 51.6, 126.0, 126.9, 128.3; u 37.6, 44.0, 145.0, 146.7. IR (cm^{-1}): 2954, 1732, 1603, 1495, 1436, 1370. MS (*m*/*z*, %): 218 (M^+, 33), 186 (34), 158 (94), 143 (31), 118 (56), 115 (21), 101 (100). HRMS calcd for $C_{14}H_{18}O_2$ 218.1307, found 218:1301.

(1*R,2*R**,4*S**)-2-Methyl-4-phenylcyclopentylmethyl 4-Bromobenzenesulfonate (12).** Lithium aluminum hydride (0.14 g, 3.6 mmol) was added to an ice-cold solution of the cyclopentane **5** (0.39 g, 1.8 mmol) in THF (8 mL). After stirring at room temperature for 2 h, H_2O (1.5 mL), aqueous 10% NaOH (1.5 mL), and H_2O (5 mL) were added sequentially at 0 °C. The reaction mixture turned into a white suspension. This white suspension was filtered and the residue was rinsed with three portions of ethyl acetate (3 × 20 mL). The combined organic fitrate was concentrated to give the crude alcohol (0.3 g, 1.60 mmol) as a yellow oil. ^{1}H NMR (δ): 7.34−7.07 (m, 5 H), 3.68 (s, 3 H), 3.26 (m, 1 H), 2.60−2.03 (m, 4 H), 1.97 (m, 1 H), 1.36 (q, $J =$ 11.3 Hz, 1 H), 1.13 (d, $J = 6.3$ Hz, 3 H). ^{13}C NMR (δ): d 19.7, 37.6, 44.1, 48.9, 125.8, 126.9, 128.2; u 37.2, 44.4, 66.3, 145.8.

p-Bromobenzenesulfonyl chloride (0.25 g, 1.0 mmol) was added to a mixture of the crude alcohol (0.3 g, 1.6 mmol) in CH_2Cl_2 (2 mL) and pyridine (2 mL). After stirring for 10 h, the reaction mixture was partitioned between CH_2Cl_2 and, sequentially, 10% aqueous HCl and brine. The combined CH_2Cl_2 extract was dried (Na_2SO_2), concentrated, and chromatographed to give the desired product **8** (0.60 g) as a white solid, TLC $R_f = 0.54$ (10% ethyl acetate/petroleum ether). This white solid was recrystallized from heptane/ether (9:1) to give colorless crystals (0.56 g, 87% yield from **2**), mp = 125 °C. The relative configurations were established by X-ray crystallography. ^{1}H NMR (δ): 7.80−7.17 (m, 9 H), 4.05 (m, 2 H), 3.02 (m,1 H), 2.20 (m, 1 H), 2.0−1.71 (m, 4 H), 1.34 (q, $J = 11.7$ Hz, 1 H), 1.05 (d, $J = 6.5$ Hz, 3 H). ^{13}C NMR (δ): d 19.2, 37.8, 34.8, 45.7, 126.0, 126.8, 128.3, 129.3, 132.6; u 36.9, 44.1, 73.7, 128.9, 135.2, 145.0; IR (cm^{-1}): 3026, 2951, 1573, 1471, 1364, 1187, 1089; MS (*m*/*z*, %): 408 (M^+, 5), 238 (10), 172 (100), 157 (88), 143 (87), 129 (41), 117 (25), 104 (73). HRMS calcd for $C_{19}H_{21}O_3SBr$ 408.0395, found 408.0395.

Ethyl 5-Phenylheptanoate (14). Triphenylphosphine (19.0 g, 71.8 mmol) and ethyl 4-bromobutyrate **13** (10.0 g, 51.3 mmol) were mixed and heated to 120 °C. After 15 min, the white solid mixture melted into a clear yellow glass. After being cooled to room temperature, the solid was dissolved with CH_2Cl_2 (6 mL) and the resultant mixture was rinsed with ether (3 × 50 mL) and dried (P_2O_5) to give the crude phosphonium salt (22.5 g, 49.2 mmol) as a white powder, mp = 143 °C. ^{1}H NMR (δ): 8.0−7.61 (m, 15 H), 4.09 (m, 2 H), 3.95 (m, 2 H), 2.94 (t, $J = 6.5$ Hz, 2 H), 2.01 (m, 2 H), 1.21 (q, $J = 7.4$ Hz, 3 H).

Sodium bistrimethylsilyamide (12.8 mL, 12.8 mmol, 1.0 M in THF) was added to a stirring solution of the above phosphonium salt (5.3 g, 11.6 mmol) in THF (35 mL) at −5 °C. After stirring for 10 min, the orange ylide was chilled to −75 °C and propiophenone (1.7 mL, 12.8 mmol) was added. The reaction mixture was allowed to warm to room temperature over 6 h, then was quenched with saturated aqueous NH_4-Cl (20 mL). The organic phase was separated and the aqueous phase was extracted with 40% ethyl acetate/petroleum ether (3 × 30 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the coupled alkene ester (1.81 g) as a colorless oil, TLC $R_f = 0.70$ (10% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 7.28−7.0 (m, 5 H), 5.41 (m, 1 H), 4.11 (q, $J = 7.1$ Hz, 2 H), 2.38−2.20 (m, 6 H), 1.23 (t, $J = 7.1$ Hz, 3 H), 0.97 (t, $J = 6.5$ Hz, 3 H); ^{13}C NMR (δ): d 12.9, 14.2, 123.5, 126.5, 128.1, 128.2; u 24.4, 32.1, 34.7, 60.2, 141.0, 144.2, 173.5. MS (*m*/*z*, %): 232 (M^+, 35), 187 (10), 157 (14), 145 (48), 129 (100), 115 (29). HRMS: calcd for $C_{15}H_{20}O_2$, 232.1464, found 232.1473.

The above alkene ester (1.07 g, 4.6 mmol) was added to a solution of palladium on carbon (0.2 g, 10%) in ethanol (10 mL). The reaction mixture was stirred under an atmosphere of H_2. After the uptake of H_2 had ceased (9 h), the reaction mixture was filtered with Celite and the filtrate was concentrated in vacuo. The trace of unhydrogenated alkene was removed by ozonolysis. Thus, the concentrated residue was diluted with 2:1 CH_2Cl_2/ethanol (40 mL). A stream of ozone was passed through the reaction mixture at −75 °C until the solution turned pale blue. The ozone was turned off and the reaction mixture was flushed with N_2. $NaBH_4$ (0.1 g, 2.63 mmol) was added to the reaction mixture which was then warmed to room temperature. After 2 h, the reaction mixture was quenched with 10% aqueous HCl (10 mL) and diluted with CH_2Cl_2 (20 mL). The organic extract was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried (Na_2SO_4), concentrated, and chromatographed to give the ethyl ester **14** (0.89 g, 53% yield from **13**) as a colorless oil, TLC $R_f = 0.70$ (10% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 7.30−7.11 (m, 5 H), 4.09 (q, $J = 7.1$ Hz, 2 H), 2.40 (m, 1 H), 2.22 (t, $J = 7.5$ Hz, 2 H), 1.80−1.41 (m, 6 H), 1.21 (t, $J = 7.1$ Hz, 3 H), 0.76 (t, $J =$7.4 Hz, 3 H). ^{13}C NMR (δ): d 12.1, 14.2, 47.6, 125.9, 127.7, 128.2; u 23.1, 29.6, 34.4, 35.8, 60.1, 145.3, 173.6. IR (cm^{-1}): 2931, 1733, 1692, 1452, 1373, 1155, 1036, 757. MS (*m*/*z*, %): 234 (M^+, 10), 206 (63), 188 (30), 156 (26), 131 (21),

117 (100). HRMS calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1617. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found C, 76.77; H, 9.71.

Methyl 2-Diazo-5-phenylheptanoate (2). Sodium hydride (0.37 g, 9.36 mmol, 60% in mineral oil), methyl benzoate (0.80 mL, 6.24 mmol), and 2 drops of CH_3OH were added sequentially to an ice-cold solution of ester **14** (0.73 g, 3.12 mmol) in DME (15 mL). The reaction mixture was heated to reflux for 12 h, then was cooled to room temperature. The reaction mixture was quenched with a solution of acetate buffer (8 mL, 0.25 M, pH = 5), then was diluted with ethyl ether (10 mL). The organic phase was separated and the aqueous phase was extracted with 30% ethyl acetate/petroleum ether (3 × 30 mL). The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The oily residue was dissolved in CH_3OH (15 mL). K_2CO_3 (0.90 g, 6.52 mmol) was added to the reaction mixture, and the mixture was heated to reflux for 8 h, then was cooled to room temperature. The reaction mixture was filtered and the filtrate was concentrated and chromatographed to give the diastereomeric methyl benzoyl esters (0.86 g, 85% yield) as pale yellow oil, TLC R_f = 0.48 (10% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 7.94−7.0 (m, 10 H), 4.21 (m, 1 H), 3.63 (2s, total 3 H), 2.41 (m, 1 H), 2.02−1.42 (m, 6 H), 0.72 (m, 3 H). ^{13}C NMR (δ): d 12.0, 47.5, 47.8, 52.4, 53.9, 56.2, 126.1, 127.7, 128.3, 128.5, 128.7; u 27.1, 27.2, 29.6, 29.8, 33.8, 34.1, 136.1, 144.7, 144.9, 170.3, 170.4, 194.9, 195.2.

1,8-Diazabicyclo[5.4.0]undec-7-ene (0.2 mL, 1.3 mmol) and 4-nitrobenzenesulfonyl azide (0.3 g, 1.3 mmol) were added to an ice-cold solution of the methyl benzoyl ester (0.22 g, 0.68 mmol) in CH_2Cl_2 (4 mL). After stirring for 1 h with warming to room temperature, aqueous phosphate buffer (3 mL, 0.5 M, pH = 7) was added and stirring was continued for an additional 30 min. The reaction mixture was partitioned between CH_2Cl_2 and brine. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the desired diazo compound **2** (0.17 g, 83% yield from **14**) as a bright yellow oil, TLC R_f = 0.53 (10% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 7.38−7.09 (m, 5 H), 3.73 (s, 3 H), 2.45 (m, 1 H), 2.16 (m, 2 H), 2.0−1.60 (m, 4 H), 0.77 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (δ): d 12.1, 47.1, 51.8, 126.2, 127.6, 128.4; u 21.4, 29.8, 34.1, 144.4, 167.7. IR (cm^{-1}): 2928, 2080, 1695, 1494, 1437, 1354, 1190, 1129, 701. MS (*m*/*z*, %): 218 ($M^+ - N_2$, 3), 187 (4), 157 (9), 129 (12), 128 (13), 120 (10), 119 (100), 117 (8), 115 (12), 103 (7), 100 (38). HRMS calcd for $C_{14}H_{18}O_2N_2$ 246.1369 (218.1307 loss of N_2), found 218.1311.

Methyl (1*R,2*R**,3*S**)-2-Methy-3-phenylcyclopentanecarboxylate (6).** A solution of dry CH_2Cl_2 (7 mL) was passed through a pad of K_2CO_3 into the bright yellow diazo compound **2** (110.9 mg, 0.45 mmol). A catalytic amount of rhodium octanoate (1 mg, 1.31 μmol) was added to this bright yellow reaction mixture. The mixture was instantly decolorized with the evolution of gas. After the gas evolution had ceased (5 min), the reaction mixture was concentrated and chromatographed to yield a mixture (80.15 mg, 87%) of cyclized and eliminated esters (2.6:1 by ^{1}H NMR integration).

This mixture was then diluted with 2:1 CH_2Cl_2/CH_3OH (8 mL). A stream of ozone was passed through the reaction mixture at −75 °C until the solution turned pale blue. The reaction mixture was flushed with N_2, then sodium borohydride (0.1 g, 2.6 mmol) was added and the cooling bath was removed. After 2 h, 10% aqueous HCl was added to quench the reaction. The resultant mixture was partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The pale brown oily residue was chromatographed, eluting with 3% ethyl acetate/petroleum ether, to give the cyclized product **6** (60.44 mg, 62% yield from **2**) as a clear pink oil, TLC R_f = 0.48 (10% ethyl acetate/petroleum ether) followed by the alcohol (16.86 mg, 23% yield from the ozonized byproduct alkene **15**).

Alcohol. TLC R_f = 0.31 (10% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 7.36−7.04 (m, 5 H), 3.71 (t, J = 6.8 Hz, 2 H), 2.83 (m, 1 H), 1.67 (m, 2 H), 1.43 (s br, 1 H), 1.26 (m, 2 H), 0.88 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (δ): d 128.5, 127.9, 126.7, 47.3, 14.1; u 143.0, 67.6, 35.2, 20.2; IR (cm^{-1}): 3348 (br), 2871, 1607, 1490, 1455. MS (*m*/*z*, %): 165 ($M^+ - H^+$, 2), 164 (10), 147 (14), 134 (25), 133 (39), 105 (13). HRMS calcd for $C_{11}H_{16}O$ 164.1202, found 164.1211.

6. ^{1}H NMR (δ): 7.41−7.10 (m, 5 H), 3.71 (s, 3 H), 2.53 (m, 2 H), 2.26−1.89 (m, 4 H), 2.0−1.83 (m, 1 H), 0.95 (d, J = 6.4 Hz, 3 H). ^{13}C NMR (δ): d 17.2, 46.8, 51.6, 51.6, 54.5, 126.3, 127.5, 128.4; u 28.2, 34.0, 143.5, 176.6. IR (cm^{-1}): 2954, 2871, 1733, 1435, 1161. MS (*m*/*z*, %): 218 (M^+, 89), 187 (26), 158 (63), 132 (33), 117 (100), 104 (73). HRMS calcd for $C_{14}H_{18}O_2$ 218.1307, found 218.1311.

Methyl (2*S*,3*S*)-2-Ethyl-3-hydroxy-7-methyl-6-octenoate. *n*-Butyllithium (74 mL, 0.17 mol, 2.31 M in hexane) was added to a stirring solution of diisopropylamine (19.0 g, 0.18 mol) in THF (150 mL) at −75 °C. After warming up to −50 °C, β-hydroxy ester **16** (14.4 g, 77.4 mmol) was added neat and the temperature was raised to −30 °C. Iodoethane (8.7 mL, 0.1 mol) in HMPA (60 mL) was added, and the reaction mixture was stirred with warming to room temperature over 4 h. Saturated aqueous NH_4Cl (60 mL) was added to quench the reaction mixture. The organic layer was separated and the aqueous layer was extracted with 30% ethyl acetate/petroleum ether. The combined extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed with 8% ethyl acetate/petroleum ether to give the desired alkylated product (10.8 g, 70% yield) as a pale yellow oil, TLC R_f = 0.51 (20% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 5.10 (m, 1 H), 3.71 (s, 3 H), 3.69 (m, 1 H), 2.53 (d, J = 8.0 Hz, 1 H), 2.20 (m, 3 H), 1.76 (m, 2 H), 1.71 (s, 3 H), 1.63 (s, 3 H), 1.48 (m, 2 H), 0.92 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (δ)SPCLN d 11.8, 17.6, 25.7, 51.5, 52.6, 71.6, 123.7; u 22.7, 24.3, 35.5, 132.3, 176.0. IR (cm^{-1}): 3465, 1736, 1670, 1437, 1376, 1171. MS (*m*/*z*, %): 214 (M^+, 1), 196 (52), 137 (24), 136 (93), 131 (22), 125 (20), 121 (39), 113 (43), 107 (46), 102 (100). HRMS calcd for $C_{12}H_{22}O_3$ 214.1569, found 214.1573.

(4*S*,5*R*)-2,2-Dimethyl-5-ethyl-4-(4-methyl-3-pentenyl)-1,3-dioxane (17). Lithium aluminum hydride (2.3 g, 61.0 mmol) was added to a solution of the above alkylated β-hydroxy ester (6.1 g, 30.5 mmol) in THF (75 mL). The reaction mixture was heated to reflux for 10 h, then was cooled to 0 °C. H_2O (3 mL), 10% aqueous NaOH (3 mL), and H_2O (9 mL) were added sequentially to the grayish reaction mixture over a period of 1 h. Substantial gas and heat evolution were observed, and the reaction mixture turned into a white paste. The reaction mixture was filtered with ethyl acetate and the filtrate was concentrated to give the desired crude diol (5.6 g). ^{1}H NMR (δ)SPCLN 5.17 (m, 1 H), 3.91 (m, 1 H), 3.69 (m, 2 H), 3.03 (br s, 1 H), 2.82 (br s, 1 H), 2.11 (m, 2 H), 1.73 (s, 3 H), 1.65 (s, 3 H), 1.60 (m, 2 H), 1.41 (m, 3 H), 0.96 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (δ)SPCLN d 11.6, 17.6, 25.0, 46.0, 75.5, 123.9; u 21.4, 24.4, 35.5, 63.6, 132.3.

p-Toluenesulfonic acid monohydrate (1.2 g, 6.1 mmol) was added to a stirring solution of the crude diol (5.6 g) in dimethoxypropane (70 mL). After 0.5 h, $NaHCO_3$ (1.3 g, 15.3 mmol) was added to neutralize the reaction mixture. The reaction mixture was filtered and the filtrate was concentrated and chromatographed directly to give **17** (5.8 g, 53% yield from **16**) as a pale yellow oil, TLC R_f = 0.89 (10% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 5.09 (m, 1 H), 3.86 (dd, J = 5.0, 11.6 Hz, 1 H), 3.51 (m, 2 H), 2.18 (m, 2 H), 1.68 (s, 3 H), 1.61 (s, 3 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.38 (m, 2 H), 1.07 (m, 2 H), 0.86 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (δ): d 10.9, 17.8, 19.3, 25.7, 29.5, 40.4, 72.5, 124.3; u 21.0, 23.4, 33.1, 64.0, 97.9, 131.5. IR: (cm^{-1}): 2926, 2859, 1457, 1379, 1264, 1199. MS (*m*/*z*, %): 226 (M^+, 3), 211 (M^+-CH_3, 20), 168 (55), 150 (50), 135 (48), 121 (88), 111 (100), 109 (52), 107 (29). HRMS calcd for $C_{14}H_{26}O_2$: 226.1934 (211.1699 loss of CH_3), found 211.1695.

Methyl (4*S*,5*R*)-2,2-Dimethyl-5-ethyl-1,3-dioxane-4-propionate (18). A stream of ozone was passed through a solution of **17** (5.4 g, 24.1 mmol) in CH_2Cl_2 (250 mL) at −75 °C. After 20 min, the red indicator (Sudan Red) was decolorized, and the ozone was turned off. The reaction mixture was flushed with N_2, and triphenylphosphine (7.6 g, 28.9 mmol) was added. The mixture was allowed to warm to room temperature over 10 h. The reaction mixture was then concentrated and the residue was dissolved in 1:9 H_2O/CH_3OH (60 mL). $NaHCO_3$ (40 g, 0.48 mol) and Br_2 (5 mL, 96.3 mmol, 1.95 M in 1:9 H_2O/CH_3OH) were added sequentially to the reaction mixture, turning the mixture bright orange. After stirring for 10 min, $Na_2S_2O_3 \cdot 5H_2O$ (36.0 g, 0.14 mol) was added. The orange reaction mixture decolorized instantly with evolution of gas. The reaction mixture was partitioned between ether and brine. The combined ethereal extract was dried (Na_2SO_4), concentrated, and chromatographed to give the ester **18** (4.3 g, 78% yield from **17**) as colorless oil, TLC R_f = 0.68 (20% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 3.88 (dd, J = 4.4, 11.6 Hz, 1 H), 3.68 (s, 3 H), 3.52 (m, 2 H), 2.43 (m, 2 H), 2.07 (m, 1 H), 1.68 (m, 1 H), 1.49 (m, 2 H), 1.39 (s, 3 H), 1.35 (s, 3 H), 1.09 (m, 1 H), 0.87 (t,

J = 7.3 Hz, 3 H). ^{13}C NMR (δ): d 10.9, 19.3, 29.4, 40.4, 51.4, 72.4; u 20.9, 28.3, 29.7, 63.9, 98.0, 174.3. IR (cm^{-1}): 2965, 1740, 1438, 1380, 1201, 1165, 1124, 868. MS (*m*/*s*, %): 215 ($M^+ - CH_3$, 45), 172 (10), 156 (7), 155 (71), 141 (52), 140 (21), 123 (100), 117 (92), 113 (29), 111 (60), 110 (25), 101(7). HRMS calcd for $C_{12}H_{22}O_4$ 230.1518 (215.1284 loss of CH_3), found 215.1279. Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H 9.63. Found C, 62.89; H 9.76.

Methyl (4*S*,5*R*)-α-Diazo-2,2-dimethyl-5-ethyl-1,3-dioxanepropionate (3). Sodium hydride (0.6 g, 15 mmol, 60% in mineral oil), methyl benzoate (1.36 g, 10.0 mmol), and 2 drops of CH_3OH were added sequentially to an ice-cold solution of ester **18** (1.15 g, 5.0 mmol) in DME (25 mL). The grayish mixture was heated to reflux for 13 h, during which time it turned dark brown. Aqueous acetate buffer (7 mL, 0.25 M, pH = 5) was added to the reaction mixture, followed by ether (15 mL). The organic layer was separated and the aqueous layer was extracted with 30% ethyl acetate/petroleum ether (3 × 20 mL). The combined organic extract was dried ($NaSO_4$), concentrated, and chromatographed to give the diastereomeric benzoyl esters (1.5 g, 93% yield) as a yellow oil, TLC R_f = 0.42 (20% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 8.14−7.23 (m, 5 H), 3.86 (m, 1 H), 3.36, 3.73 (2s, total 3 H), 3.70−3.37 (m, 2 H), 2.70−2.41 (m, 1 H), 2.07−1.78 (m, 1 H), 1.48 (m, 2 H), 1.34−1.23 (4s, total 6 H), 1.09 (m, 2 H), 0.91 (t, J= 7.4 Hz, 3 H).

DBU (1.3 mL, 8.6 mmol) and 4-nitrobenzenesulfonyl azide (2.0 g, 8.6 mmol) were added sequentially to a solution of the benzoyl ester (1.4 g, 4.4 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After warming to room temperature (0.5 h), the reaction mixture was quenched with aqueous phosphate buffer (13 mL, 0.5 M, pH = 7). The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give **3** (1.4 g, 78% from **18**) as a bright yellow oil, TLC R_f = 0.43 (10% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 3.89 (dd, J = 5.8, 11.6 Hz, 1 H), 3.76 (s, 3H), 3.74 (m, 1 H), 3.56 (t, J = 11.6 Hz, 1 H), 2.68 (dd, J = 2.9, 15.2 Hz, 1 H), 2.41 (dd, J = 7.0, 15.2 Hz, 1 H), 1.56 (m, 4 H), 1.59 (s, 3 H), 1.55 (s, 3 H), 0.89 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (δ): d 27.6, 36.1, 46.1, 56.0, 58.6, 90.1; u 33.8, 37.7, 43.6, 80.5, 114.9, 167.9. IR (cm^{-1}): 2960, 2078, 1699, 1437, 1221. MS (*m*/*s*, %): 228 ($M^+ - N_2$, 3), 213 (19), 198 (74), 197 (24), 183 (6), 140 (13), 117 (100). HRMS calcd for $C_{12}H_{20}O_4N_2$ 256.1424 (228.1362 loss of N_2), found 228.1366.

Methyl (1*S*,2*S*,3a*S*,7a*R*)-1,5,5-Timethyl-4,6-dioxa-(2,3,3a,4,5,6,7,7a)-octahydroindene-2-carboxylate (7). CH_2Cl_2 (40 mL) was passed through a pad of K_2CO_3 into the bright yellow diazo ester **3** (2.1 g, 8.2 mmol). A catalytic amount of Rh_2Oct_4 (0.9 mg, 1.16 μmol) was added to the reaction mixture. The mixture was decolorized instantly with evolution of gas. After the gas evolution had ceased (5 min), the mixture was concentrated and chromatographed directly to give a single diastereomer **7** (1.8 g, 89% yield from **3**) as a pale yellow oil, TLC R_f = 0.38 (10% ethyl acetate/petroleum ether). The relative configuration was established by NOE experiments. ^{1}H NMR (δ): 3.89 (dd, J = 5.8, 11.6 Hz, 1 H), 3.80 (m, 2 H), 3.61 (s, 3 H), 2.44 (m, 1H), 2.26 (m, 1 H), 1.81 (m, 2 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 1.31 (m, 1 H), 1.16 (d, J = 7.6 Hz, 3 H). ^{13}C NMR (δ): d 18.3, 19.7, 29.7, 36.9, 47.0, 49.1, 51.9, 73.8; u 32.7, 65.5, 99.5, 176.6. IR (cm^{-1}): 2954, 1735, 1459, 1381, 1264, 1178, 1113. MS (*m*/*z*, %): 213 ($M^+ - CH_3$, 42), 153 (11), 139 (33), 127 (30), 121 (21), 111(49), 93 (100). HRMS calcd for $C_{12}H_{20}O_4$ 228.1362 (213.1127 loss of CH_3), found 213.1132.

Ethyl (2*S,3*S**)-2-(1-Hydroxybutyl)-4-pentenoate (20).** *n*-Butyllithium (76 mL, 0.17 mol, 2.18 M in hexane) was added to a solution of diisopropylamine (25.3 mL, 0.18 mol) in THF (200 mL) at −75 °C. After warming up to −60 °C, ethyl acetate (13.5 mL, 0.14 mol) followed by n-butyraldehyde (**19,** 12.5 mL, 0.14 mol) were added. After the mixture was stirred for 2 h with warming to room temperature, saturated aqueous NH_4Cl (80 mL) was added. The organic layer was separated and the aqueous layer was extracted with 40% ethyl acetate/petroleum ether (3 × 80 mL). The combined organic extract was dried ($MgSO_4$), concentrated, and chromatographed to give the desired β-hydroxy ester (13.54 g, 61% yield) as a colorless oil, TLC R_f = 0.37 (20% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 4.18 (q, J = 7.2 Hz, 2 H), 4.02 (m, 1 H), 3.06 (br s, 1 H), 2.55−2.28 (m, 2 H), 1.62−1.28 (m, 4 H), 1.29 (t, J = 7.2 Hz, 3 H), 0.94 (t, J = 6.9 Hz, 3 H).

n-Butyllithium (24 mL, 32.4 mmol, 2.18 M in hexane) was added to a stirring solution of diisopropylamine (7.6 mL, 55.0 mmol) in THF (25 mL) at −75 °C. After the reaction mixture was warmed to −50 °C, β-hydroxy ester (4.0 g, 25.0 mmol) was added. At −20 °C, allyl bromide (2.4 mL, 27.4 mmol) in 6 mL of HMPA was added to the reaction mixture. After stirring in room temperature for 4 h, the reaction mixture was partitioned between 40% ethyl acetate/petroleum ether and saturated aqueous NH_4Cl. The combined organic phase was dried ($MgSO_4$), concentrated, and chromatographed to afford **20** (3.35 g, 41% yield from **19**) as a colorless oil, TLC R_f = 0.41 (20% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 5.78 (m, 1 H), 5.06 (m, 2 H), 4.18 (q, J = 7.2 Hz, 2 H), 3.71 (m, 1 H), 2.62 (d, J = 8.0 Hz, 1 H), 2.46 (m, 3 H), 1.63−1.42 (m, 4 H), 1.30 (t, J = 7.2 Hz, 3 H), 0.93 (t, J = 6.9 Hz, 3 H). ^{13}C NMR (δ): d 13.9, 14.2, 50.4, 71.5, 134.9; u 18.9, 33.8, 37.7, 60.5, 117.1, 174.9. IR (cm^{-1}): 3464 (br), 2959, 2874, 1733, 1642, 1470, 1377, 1180. MS (*m*/*z*, %): 200 (M^+, 16), 182 (21), 157 (72), 129 (34), 128 (60), 111 (37), 109 (37), 100 (100). HRMS calcd for $C_{10}H_{18}O_3$ 200.1413, found 200.1422.

(4*S,5*R**)-2,2-Dimethyl-5-(2-propenyl)-4-propyl-1,3-dioxane (21).** Lithium aluminum hydride (1.71 g, 45.0 mmol) was added to an ice-cold solution of **20** (3.0 g, 15.0 mmol) in THF (75 mL). The grayish reaction mixture was heated to reflux for 13 h, then was cooled to 0 °C. H_2O (2 mL), 10% aqueous NaOH (2 mL), and H_2O (6 mL) were added sequentially to the grayish mixture, turning it into a white suspension. This white suspension was filtered and the residue was rinsed with ethyl acetate. The combined filtrate was concentrated to give the crude diol (2.25 g). ^{1}H NMR (δ): 5.81 (m, 1 H), 5.16 (m, 2 H), 3.93 (m, 1 H), 3.76 (m, 2 H), 2.80−2.37 (m, 2 H), 2.29−2.07 (m, 2 H), 1.83−1.03 (m, 5 H), 0.95 (t, J = 6.9 Hz, 3 H).

p-TsOH·H_2O (0.57 g, 3.0 mmol) was added to a stirring solution of the above crude diol (2.25 g) in dimethyoxypropane (30 mL). After 10 min, $NaHCO_3$ (1.26 g, 15.0 mmol) was added, and stirring was continued for an additional hour. The reaction mixture was filtered, and the filtrate was concentrated and chromatographed to give **21** (2.64 g, 89%) as a colorless oil, TLC R_f = 0.87 (10% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 5.71 (m, 1 H), 5.06 (m, 2 H), 3.74 (dd, J = 5.2 Hz, 11.6 Hz, 1 H), 3.54 (t, J = 11.6 Hz, 2 H), 2.17 (m, 1 H), 1.62−1.41 (m, 3 H), 1.41−1.23 (m, 3 H), 1.41 (s, 3 H), 1.38 (s, 3 H), 0.90 (t, J = 6.8 Hz, 3 H). ^{13}C NMR (δ): d 14.0, 19.5, 29.3, 38.6, 72.8, 135.3; u 18.2, 33.0, 35.2, 64.0, 98.1, 116.7. IR (cm^{-1}): 2926, 2871, 1458, 1379, 1198, 1171, 995. MS (*m*/*z*, %): 184 (13), 183 ($M^+ - CH_3$, 100), 155 (11), 131 (14), 123 (36), 110 (7), 99 (8), 97 (17), 95 (19). HRMS calcd for $C_{12}H_{22}O_2$ 198.1620, found 198.1633.

Methyl (4*S,5*R**)-2,2-dimethyl-4-propyl-1,3-dioxane-5-acetate (22).** A stream of ozone was passed through a solution of **21** (2.1 g, 10.6 mmol) in CH_2Cl_2 (100 mL) at −76 °C. After 11 min, the solution turned pale blue and the ozone was turned off. The reaction mixture was flushed with N_2, and triphenylphosphine (2.80 g, 10.6 mmol) was added. The reaction mixture was warmed to room temperature for 5 h. It was then concentrated, and the residue was diluted with 9:1 CH_3OH/H_2O (45 mL). $NaHCO_3$ (3.56 g, 42.4 mmol) was added followed by a stock solution of bromine (22 mL, 1.95M in 9:1 CH_3OH/H_2O). After 10 min, $Na_2S_2O_3$·$5H_2O$ (15.8 g, 63.6 mmol) was added and the bright orange reaction mixture was decolorized with evolution of gas. H_2O (15 mL) and ethyl ether (40 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with Et_2O (3x 40 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the desired ester **22** (2.02 g, 83% yield from **21**) as a colorless oil, TLC R_f = 0.61 (20% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 3.78 (dd, J = 5.3, 11.5 Hz, 1 H), 3.66 (s, 3 H), 3.54 (m, 2 H), 2.31 (m, 1 H), 2.06 (m, 2 H), 1.52−1.24 (m, 4 H), 1.42 (s, 3 H), 1.38 (s, 3 H), 0.89 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (δ): d 13.9, 19.5, 29.1, 36.3, 51.7, 72.0; u 18.0, 33.3, 35.1, 63.7, 98.3, 172.2. IR (cm^{-1}): 2958, 2872, 1741, 1438, 1380, 1264, 1198, 1171; MS (*m*/*z*, %): 215 ($M^+ - CH_3$, 31), 172 (5), 155 (67), 141 (44), 140 (15), 129 (65), 123 (100), 113 (31), 112 (16), 110 (17), 101 (49). HRMS calcd for $C_{12}H_{22}O_4$ 230.1518 (215.1284 loss of CH_3), found 215.1290.

Methyl (4S*,5*R)-α-Diazo-2,2-dimethyl-4-propyl-1,3-dioxane-5-acetate (4).** Methyl benzoate (0.57 mL, 4.61 mmol), NaH (0.3 g, 7.50 mmol), and 2 drops of CH_3OH were added sequentially to a ice-cold solution of ester **22** (0.53 g, 2.30 mmol) in DME (12 mL). The grayish reaction mixture was warmed to reflux for 13 h. Aqueous acetate buffer

(10 mL, 0.25 M, pH = 5) and Et_2O (20 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined ethereal extract was dried (K_2CO_3), concentrated, and chromatographed to give the diastereomeric benzoyl esters (0.68 g, 89% yield) as a pale yellow oil, TLC R_f = 0.53 (20% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 8.15−7.40 (m, 5 H), 4.49 (dd, J = 4.6 Hz, 5.9 Hz, 1 H), 4.09−3.74 (m, 3 H), 3.60, 3.65 (2s, total 3 H), 2.40 (m, 1 H), 1.58−1.20 (m, 10 H), 0.87 (m, 3 H).

DBU (0.32 mL, 2.14 mmol) and 4-nitrobenzenesulfonyl azide (0.26 g, 2.14 mmol) were added sequentially to a ice-cold solution of the above benzoyl ester (0.42 g, 1.26 mmol) in CH_2Cl_2 (6 mL). After the reaction mixture was warmed to room temperature (0.5 h), the reaction mixture was quenched with aqueous phosphate buffer (4 mL, 0.5 M, pH = 7). The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined extract was dried (K_2CO_3), concentrated, and chromatographed to give the desired diazo product **4** (0.27 g, 74% yield from **22**) as a bright yellow oil, TLC R_f = 0.69 (20% ethyl acetate/petroleum ether. ^{1}H NMR (δ): 3.89 (d, J = 7.6 Hz, 1 H), 3.82 (m, 2 H), 3.77 (s, 3 H), 2.47 (q, J = 7.6 Hz, 1 H), 1.63−1.26 (m, 4 H), 1.46 (s, 3 H), 1.40 (s, 3 H), 0.90 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (δ): d 13.9, 19.4, 29.1, 35.2, 52.0, 69.8; u 18.1, 29.7, 36.0, 61.8, 98.6, 166.9. IR (cm^{-1}): 2958, 2873, 2087, 1701, 1437, 1338, 1199, 1134. MS (*m*/*z*, %): 213 ($M^+ - CH_3 - N_2$, 8), 185 (11), 170 (14), 153 (26), 139 (24), 138 (30), 127 (100), 121 (15), 111 (33), 110 (17). HRMS calcd for $C_{12}H_{20}O_4N_2$ 256.1424 (228.1362 loss of N_2), found 228.1377.

Methyl (1*S,2*R**,3a*S**,7a*R**)-2,5,5-Timethyl-4,6-dioxa-(2,3,3a,4,-5,6,7,7a)-octahydroindene-1-carboxylate (8).** CH_2Cl_2 (5 mL) was passed through a pad of K_2CO_3 into the bright yellow diazo ester **4** (110.0 mg, 0.43 mmol). A catalytic amount of Rh_2Oct_4 (0.9 mg, 1.16 μmol) was added to the reaction mixture. The mixture was instantly decolorized with evolution of gas. After the gas evolution had ceased (6 min), the mixture was concentrated and chromatographed directly to give a single diastereomer **8** (89.2 mg, 91% yield from **4**) as a pale yellow oil, TLC R_f = 0.41 (10% ethyl acetate/petroleum ether). ^{1}H NMR (δ): 4.02−3.80 (m, 3 H), 3.67 (s, 3 H), 2.47 (m, 2H), 2.26 (m, 1 H), 1.95 (m, 1 H), 1.46 (s, 3 H), 1.42 (s, 3 H), 1.91 (m, 1 H), 1.15 (d, J = 7.9 Hz, 3 H). ^{13}C NMR (δ): d 19.7, 22.0, 29.6, 32.6, 43.5, 48.6, 51.5, 72.5; u 38.8, 63.6, 99.2, 174.8. IR (cm^{-1}): 2956, 2872, 1732, 1459, 1380, 1265, 1167. MS (*m*/*z*, %): 213 ($M^+ - CH_3$, 18), 153 (9), 139 (39), 127 (11), 121 (13), 111 (39), 110 (54), 100 (100). HRMS calcd for $C_{12}H_{20}O_4$ 228.1362 (213.1127 loss of CH_3), found 213.1119.

Lactone 23. *p*-TsOH·H_2O (80.1 mg, 0.43 mmol) was added to a stirring solution of **8** (89.2 mg, 0.39 mmol) in THF (3 mL). After 0.5 h, the reaction mixture was partitioned between ether and saturated aqueous $NaHCO_3$. The combined organic phase was dried (Na_2SO_4), concentrated, and chromatographed to give lactone **23** (54.3 mg, 99% yield from **8**) as a pale yellow oil, TLC R_f = 0.47 (10% ethyl acetate/petroleum ether). The relative configurations was established by NOE experiments. ^{1}H NMR (δ): 4.43 (dd, J = 7.4, 9.7 Hz, 1 H), 4.23 (dd, J = 2.8 Hz, 9.7 Hz, 1 H), 4.11 (q, J = 7.7 Hz, 1 H), 2.87 (m, 1 H), 2.69 (dd, J = 5.1, 9.9 Hz, 1 H), 2.35 (m, 1 H), 2.17 (m, 2 H), 1.46 (m, 1 H), 1.27 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (δ): d 21.7, 36.2, 48.4, 49.7, 78.7; u 44.0, 70.8, 180.0. IR (cm^{-1}): 3422 (br), 2960, 2872, 1765, 1458, 1378, 1181, 1088, 1050. MS (*m*/*z*, %): 157 ($M^+ + H^+$, 2), 113 (3), 112 (4), 110 (3), 97 (10), 95 (2), 85 (15), 84 (100). HRMS calcd for $C_8H_{12}O_3$ 156.0786, found 156.0809.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds (40 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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