minor lactone **22** as a white solid, mp 122–124 °C, 60 mg (4% yield) of more of **21**, and 50 mg of recovered starting material. Spectral data for the major lactone **21**: $[\alpha]_D$ −78° (*c* 0.35, DMF); IR (KBr) 3500, 3300, 1770, 1720, 1680, 1600 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, room temperature) δ 1.39 (br s, 9 H), 4.05 (t, *J* = 8.0 Hz, H), 4.13 (dd, *J* = 7.0 and 6.1 Hz, H), 4.24 (dd, *J* = 12.5 and 1.9 Hz, H), 4.48 (dd, *J* = 7.0 and 6.1 Hz, H), 4.66 (ddd, *J* = 7.0, 6.3, and 1.9 Hz, H), 5.91 (d, *J* = 5.2 Hz, H, exchanged with D_2O), 6.59 (br s, 2 H, exchanged slowly with D_2O), 7.52 (d, *J* = 8.1 Hz, H, exchanged slowly with D_2O); ^{13}C NMR (pyridine-d_5, room temperature) δ 28.38, 58.61, 63.12, 71.95, 79.10, 79.34, 156.90, 157.74, 174.04. Anal. Calcd for $C_{11}H_{18}N_2O_7$: C, 45.51; H, 6.25; N, 9.65. Found: C, 45.54; H, 6.10; N, 9.64. Spectral data for the minor lactone **22**: $[\alpha]_D$ +48° (*c* 0.77, DMF); IR (KBr) 3500, 3300, 1700, 1720, 1680, 1600 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, room temperature) δ 1.40 (s, 9 H), 4.03 (dd, *J* = 12.3 and 8.8 Hz, H), 4.20 (dd, *J* = 12.3 and 4.2 Hz, H), 4.26 (dd, *J* = 4.5 and 3.2 Hz, H), 4.64 (dt, *J* = 8.8 and 2.8 Hz, H), 4.72 (dd, *J* = 9.2 and 4.8 Hz, H), 5.72 (d, *J* = 5.7 Hz, H, exchanged with D_2O), 6.54–6.71 (br s, 2 H, exchanged slowly with D_2O), 6.66 (d, *J* = 9.2 Hz, H, exchanged slowly with D_2O); ^{13}C NMR (pyridine-d_5, room temperature) δ 28.40, 56.88, 63.74, 69.61, 79.18, 80.36, 156.93, 157.99, 175.20. Anal. Calcd for $C_{11}H_{18}N_2O_7$: C, 45.51; H, 6.25; N, 9.65. Found: C, 45.41; H, 6.09; N, 9.61.

2-Amino-2-deoxy-L-xylonic Acid, γ-Lactone, 5-Carbamate, Mono(trifluoroacetate) (Salt) (23) and 2-Amino-2-deoxy-L-lyxonic Acid, γ-Lactone, 5-Carbamate, Mono(trifluoroacetate) (Salt) (26). A mixture of lactone **21** (6.0 mg, 0.021 mmol) in 4% trifluoroacetic acid/CH_2Cl_2 was stirred at room temperature for 3–4 h at which time the TLC in EtOAc showed the clean formation of product, R_f 0.06, at the expense of starting material, R_f 0.42. The solvent was evaporated to leave 6.9 mg of **23** as a white solid, mp 138–140 °C: IR (KBr) 3440, 3300, 1790, 1700, 1650, 1580 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 4.35 (dd, *J* = 12.7 and 2.6 Hz, H-5), 4.38 (dd, *J* = 12.7 and 2.8 Hz, H-5′), 4.42 (d, *J* = 9.5 Hz, H-2), 4.86 (dd, *J* = 9.5 and 8.1 Hz, H-3), 4.94 (ddd, *J* = 8.1, 2.8, and 2.6 Hz, H-4). Anal. Calcd for $C_8H_{11}N_2O_7F_3$: C, 31.59; H, 3.65; N, 9.21. Found: C, 31.55; H, 3.51; N, 8.86. In a similar manner, treatment of **22** with TFA afforded 6.9 mg of the diastereomeric triflate salt **26** as a white solid, mp 140–141 °C: IR (KBr) 3430, 3300, 1800, 1660, 1600 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 4.32 (dd, *J* = 12.3 and 7.7 Hz, H-5), 4.33 (dd, *J* = 12.3 and 3.9 Hz, H-5′), 4.54 (d, *J* = 5.0 Hz, H-2), 4.78 (dd, *J* = 5.0 and 2.8 Hz, H-3), 4.83 (ddd, *J* = 7.7, 3.9, and 2.8 Hz, H-4).

2-Amino-2-deoxy-L-xylonic Acid, 5-Carbamate (5-*O*-Carbamoylpolyoxamic Acid), Hydrochloride (25). A stirred mixture of lactone **21** (49.7 mg, 0.170 mmol) in 1 N HCl (5.0 mL) was heated at 95 °C for 1 h when the TLC in (3.6:3.6:2.1:0.7) pyridine–EtOAc–H_2O–HOAc showed clean formation of a product that corresponded to 5-*O*-carbamoylpolyoxamic acid (**2**), R_f 0.30. A small amount of an intermediate lactone corresponding to **24**, R_f 0.76, was also detected. The reaction mixture was cooled, and the solvent was removed in vacuo to afford 45.3 mg of product as a crystalline foam, which decomposed at 150 °C, $[\alpha]_D$ −6.2°, $[\alpha]_{365}$ −23° (*c* 0.76, H_2O). IR (KBr) 3700–2300 br, 1780 (lactone salt), 1720, 1590 cm^{-1}; ^1H NMR of **25** (400 MHz, D_2O + DCl, pD = 2.0, room temperature) δ 4.06 (br s, 3 H), 4.08 (d, *J* = 3.4 Hz, H), 4.24 (ddd, *J* = 3.4, 1.5, and 0.6 Hz, H-4). This spectrum also showed the presence of a small amount of lactone salt **24** whose signals matched those reported for **23** (vide supra). The overall ratio of **25** to **24** was determined to be (4:1) by integration. The NMR spectrum of synthetic **25** was identical with one obtained with an authentic sample of 5-*O*-carbamoylpolyoxamic acid (**2**) in D_2O + DCl.

Acknowledgment. This work was supported by Public Health Service Grant GM 35557 administered by the National Institute of General Medical Sciences. We thank Dr. Kiyoshi Isono for providing us with an authentic sample of **2** for comparison and Dr. Kurt Loening for assistance with the nomenclature.

Registry No. **6**, 95715-87-0; **7**, 114301-34-7; **8**, 114301-35-8; **9**, 114301-36-9; **10**, 114376-27-1; **11** (isomer 1), 114301-37-0; **11** (isomer 2), 114301-51-8; **12** (isomer 1), 114301-38-1; **12** (isomer 2), 114301-39-2; **13**, 114324-28-6; **14**, 114301-40-5; **15**, 114301-41-6; **16**, 114301-42-7; **19**, 114301-43-8; **20**, 114301-52-9; **21**, 114301-44-9; **22**, 114301-45-0; **23**, 114301-47-2; **24**, 114301-50-7; **25**, 114324-36-6; **26**, 114301-49-4; (*R*)-(+)-MTPA, 20445-31-2; (*S*)-(−)-MTPA, 17257-71-5; polyoxin, 11113-80-7.

Enantioselective Ring Construction with Control of Side-Chain Stereochemistry: Synthesis of (+)-Isoneonepetalactone

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Received June 17, 1987

Intramolecular cyclopropanation of **13**, directed by R*OH **1**, proceeds with significant face selectivity, to give **14** as the major product. The influence of both transition metal catalyst and olefin substitution and geometry on the diastereomeric excess and chemical yield of this reaction has been explored. Opening of enantiomerically pure cyclopropane **8** with lithium divinylcuprate, followed by further synthetic modification, leads to (+)-isoneonepetalactone (**26**).

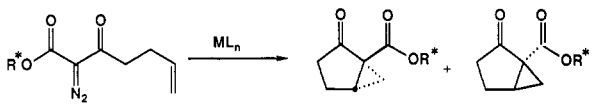
The development of new methods for ring construction is fundamental to the development of synthetic organic chemistry. In particular, as striking differences in the physiological activity of enantiomers have appeared, and as convergent design has come to dominate synthetic planning, there has been a need for the development of methods for ring construction with the control of absolute stereochemistry. While several elegant methods have appeared in recent years,[2] little work has been directed toward the development of methods for ring construction with control of side-chain stereochemistry.[3] We report

(1) Fellow of the Alfred P. Sloan Foundation, 1983–1987.

(2) Several strategies for the enantioselective preparation of carbocycles have been reported. For leading references, see: Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28.

0022-3263/88/1953-2984$01.50/0

Table I

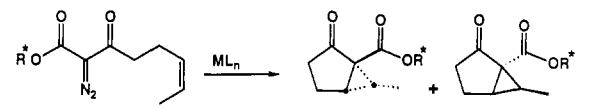


10 11 12

catalyst	ratio[a]	chemical yield,[a] %
$Cu(TBS)_2$[b]	28:72	66
$(dppe)PdCl_2$[c]	70:30	69
$(dppp)PdCl_2$[c]	28:72	57
(OEP)RhCl[d]	83:17	63
$Ru_3(CO)_{12}$[e]	66:34	66
(TPP)RhCl[d]	89:11	64

[a] Yields and ratios are for chromatographically purified products. [b] Reference 15. [c] For the preparation of $(dppe)PdCl_2$ and $(dppp)PdCl_2$, see ref 14. [d] Reference 16. [e] Commercially available.

Table II

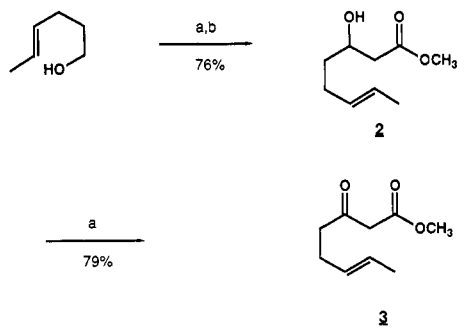


13 14 15

catalyst	ratio[a]	chemical yield,[a] %
$Cu(TBS)_2$[b]	66:34	94
$(dppp)PdCl_2$[c]	80:20	64
(OEP)RhCl[d]	63:37	51
$Ru_3(CO)_{12}$[e]	53:47	67
(TPP)RhCl[d]	68:32	43

[a] Yields and ratios are for chromatographically purified products. [b] Reference 15. [c] For the preparation of $(dppp)PdCl_2$, see ref 14. [d] Reference 16. [e] Commercially available.

Scheme I[a]

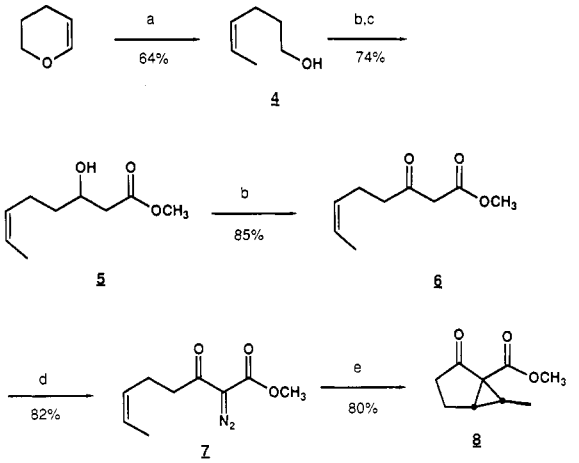


[a] Reagents: (a) Swern; (b) LDA/methyl acetate.

what promises to be a general solution to this problem.

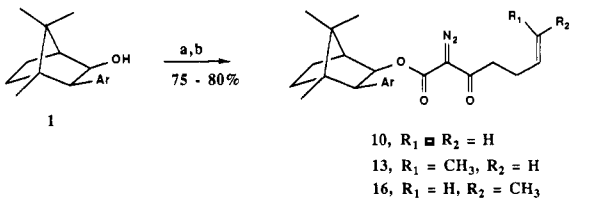
The basis for our approach is intramolecular cyclopropanation (13 → 14, Table II) followed by conjugate addition (8 → 19, Scheme V). As geometry is maintained in the first step, and as opening of the activated cyclo-

Scheme II[a]



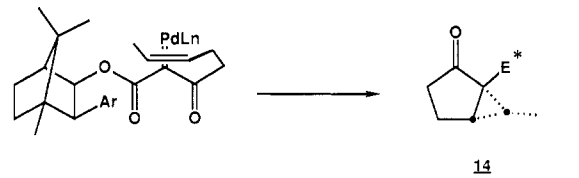
[a] Reagents: (a) $(dppp)NiCl_2$, CH_3MgBr; (b) P_2O_5/dimethyl sulfoxide; Et_3N; (c) LDA/methyl acetate; (d) mesyl azide/Et_3N; (e) $Cu(TBS)_2$ (ref 15).

Scheme III[a]

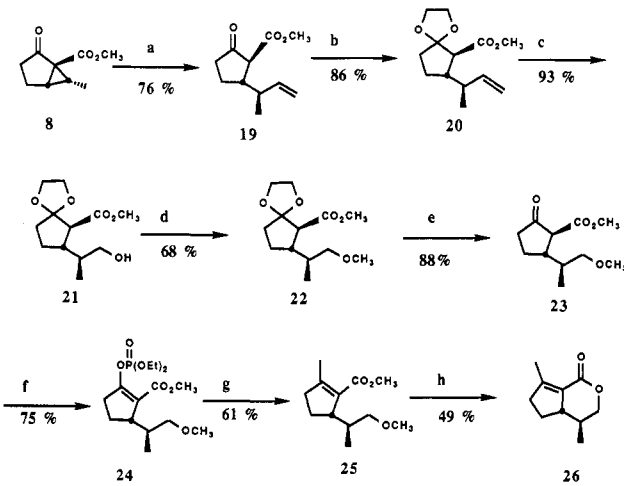


[a] (a) Methyl 3-oxo-6-heptenoate (for 10), 6 (for 13), or 3 (for 16), 4-DMAP; (b) mesyl azide/Et_3N.

Scheme IV



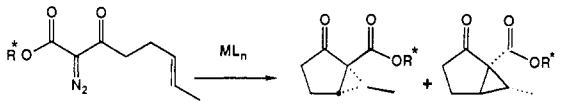
Scheme V[a]



[a] Reagents: (a) tetravinyltin, CH_3Li, CuBr·DMS, Et_2O; (b) BF_3·Et_2O, ethylene glycol, CH_2Cl_2; (c) O_3, Sudan III; $NaBH_4$; (d) Ag_2O, CH_3I, CH_3CN; (e) Dowex-50, acetone; (f) $ClP(O)(OEt)_2$, NaH, Et_2O; (g) CuI, CH_3Li, Et_2O; (h) BBr_3, 15-crown-5, CH_2Cl_2, NaI.

(3) For leading references to methods for carbocyclic ring construction with control of side-chain stereochemistry, see the following. (a) Intramolecular cyclopropanation/conjugate addition: Corey, E. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1972**, *94*, 4014. Taber, D. F.; Krewson, K. R.; Raman, K.; Rheingold, A. C. *Tetrahedron Lett.* **1984**, *25*, 5283. (b) Diastereoselective addition to a preformed ring: Ficini, J.; Guingant, A.; d'Angelo, J.; Stork, G. *Tetrahedron Lett.* **1983**, *24*, 907. Morgans, D. J., Jr.; Feigelson, G. B. *J. Am. Chem. Soc.* **1983**, *105*, 5477. Marino, J. P.; Perez, A. D. *J. Am. Chem. Soc.* **1984**, *106*, 7643. Binns, M. R.; Haynes, R. K.; Katsifis, A. A.; Schober, P. A.; Vonwiller, S. C. *Tetrahedron Lett.* **1985**, *26*, 1565. (c) Intermolecular Michael addition/ring closure: Yamaguchi, M.; Tsukamoto, M.; Hirao, I. *Tetrahedron Lett.* **1985**, *26*, 1723. Yamaguchi, M.; Hasebe, K.; Tanaka, S.; Minami, T. *Tetrahedron Lett.* **1986**, *27*, 959. (d) Intramolecular organometallic addition: Utimoto, K.; Imi, K.; Shiragami, H.; Fujikura, S.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 2101. (e) Tandem Cope rearrangement/Claisen rearrangement: Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1982**, *104*, 7181. (f) Intermolecular 1,3-dipolar cycloaddition: Büchi, G.; Chu, P.-S. *J. Am. Chem. Soc.* **1981**, *103*, 2718. (g) Intramolecular 1,3-dipolar cycloaddition: Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024.

Table III

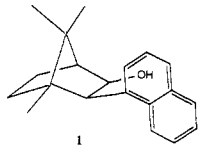


16 17 18

catalyst	ratio[a]	chemical yield,[a] %
$Cu(TBS)_2$[b]	53:47	70
$(dppp)PdCl_2$[c]	80:20	38
(OEP)RhCl[d]	63:37	59
$Ru_3(CO)_{12}$[e]	52:48	76
(TPP)RhCl[d]	70:30	55

[a] Yields and ratios are for chromatographically purified products. [b] Reference 15. [c] For the preparation of $(dppp)PdCl_2$, see ref 14. [d] Reference 16. [e] Commercially available.

propane, in the second step, proceeds cleanly with inversion at the apical carbon,[3a] this is a general method for ring construction with control of relative stereochemistry on the pendant chain. To be made *enantioselective*, it would be necessary to achieve *face-selective* cyclopropanation.[4] In this preliminary account, we report that α-diazo β-keto esters derived from naphthylborneol R*OH 1,[5] readily



1

prepared from (+)-camphor, can be induced to cyclize in good chemical yield and with reasonable diastereomeric excess.[6]

Preparation of Enantiomerically Pure β-Keto Esters. To pursue these studies, we needed α-diazo β-keto esters **10**, **13**, and **16** (Scheme III), representing the three olefin substitution patterns that would be of interest to us. We knew that such diazo esters could readily be prepared by diazo transfer[7] to the precursor β-keto esters. Several attempts to prepare β-keto esters of naphthylborneol **1** by using conventional techniques proved fruitless. We found, however, that simply heating **1** with the corresponding methyl β-keto ester, in a process catalyzed by 4-(dimethylamino)pyridine,[8] gave the desired enantiomerically pure ester in excellent yield. The problem then devolved to the preparation of the requisite methyl esters.

The simplest of the three, corresponding to the substitution pattern of **10**, had already been prepared,[9] by allylation of the dianion of methyl acetoacetate. While ester **3** (Scheme I) could have been prepared in the same way, by using crotyl chloride, we found homologation of commercially available *trans*-4-hexen-1-ol to be easier on a large scale.

We briefly explored preparation of ester **6** (Scheme II) by hydrogenation of acetylenic precursors. In all cases examined, however, the resultant alkene was at best only 95% cis. We therefore turned to the excellent method developed by Wenkert[10] for nickel-catalyzed coupling of methylmagnesium bromide[11] with dihydropyran. When this approach was used, pure *cis*-4-hexen-1-ol could readily be prepared on a 100-g scale. Homologation, as before, then gave β-keto ester **6**.

Ester exchange and diazo transfer proceeded as expected, to give α-diazo β-keto esters **10**, **13**, and **16** (Scheme III). At the same time as we were exploring diastereoselectivity in the cyclization of these esters (Tables I–III), we also developed experimental procedures for the conversion of racemic **8** (Scheme II) to isoneonepetalactone **26** (Scheme V).[12]

Studies of Intramolecular Cyclopropanation. Our goal in this preliminary investigation has been to quantitate the change in the diastereoselectivity of intramolecular cyclopropanation on changing the transition metal complex used to catalyze the reaction. The key determinant, the isolated yield of the major diastereomer, would be the product of the chemical yield of the cyclization and the diastereomeric ratio of the product. We have screened a variety of metal–ligand combinations, seeking to optimize both of these factors. Some highlights from these studies are summarized in Tables I–III. A key assumption here is that both the metal and the ligand are associated with the transition state in the product-determining step. The range of ratios observed (Tables I–III) is evidence that such must indeed be the case.

Our objective, from a practical point of view, was to achieve a 60% isolated yield of **14** from **13** (Table II). It should be noted that **14** (TLC R_f 0.33) and **15** (TLC R_f 0.24) are readily separable by simple silica gel chromatography.[13] All yields and ratios reported (Tables I–III) are for the pure isolated diastereomeric cyclopropanes.

Optimization of the cyclization turned out to be a function not just of the transition metal complex employed but also of the substitution on the olefin. In the vinyl series (Table I), it was possible to optimize for either diastereomer, while with the cis olefin (Table II) only one diastereomer could be made dominant. While product ratios for the trans olefin (Table III) were similar to those for cis (Table II), chemical yields were significantly lower when Pd catalysis was used in the trans series.

Initial assignment of the relative stereochemistry of each diastereomeric cyclopropane was effected by conversion to materials that were alternatively prepared by intramolecular CH insertion.[2] In the case of **11** and **12**, comparison was effected by conjugate addition of lithium di-*n*-butylcuprate, to give the 3-*n*-pentylcyclopentanone carboxylates. For **14** and **15**, and for **17** and **18**, comparison was effected by submitting each pure diastereomer to

(4) Methods for enantioselective cyclopropanation by *intra*molecular carbene insertion have not previously been reported. For leading references to enantioselective *inter*molecular cyclopropanation, see: (a) Aratani, T.; Yonegoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1975**, 1707. Aratani, T.; Yonegoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1977**, 2599. Aratani, T. *Kagaku, Zokan (Kyoto)* **1985**, *105*, 133; *Chem. Abstr.* **1985**, *103*, 1051616. (b) Matlin, S. A.; Lough, W. J.; Chau, L.; Abram, D. W. H.; Zhou, Z. *J. Chem. Soc., Chem. Commun.* **1984**, 1038. (c) Doyle, M. P.; Dorow, R. L.; Terpstra, J. W.; Rodenhouse, R. A. *J. Org. Chem.* **1985**, *50*, 1663.

(5) (a) For the preparation of **1**, see: Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28. (b) Concurrently with our work, others have investigated chiral induction with modified bornyl esters. For leading references, see: Helmchen, G.; Schmierer, R. *Tetrahedron Lett.* **1983**, *24*, 1235. Oppolzer, W.; Chapuis, C. *Tetrahedron Lett.* **1983**, *24*, 4665. Somfai, P.; Tanner, D.; Olsson, T. *Tetrahedron* **1985**, *41*, 5973.

(6) Cyclization of the corresponding menthyl ester proceeds to give a 1:1 mixture of diastereomers: Taber, D. F.; Saleh, S. A.; Korsmeyer, R. W. *J. Org. Chem.* **1980**, *45*, 4699.

(7) (a) Regitz, M.; Hocker, J.; Liedhegener, A. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 197. (b) Taber, D. F.; Ruckle, R. E., Jr.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077.

(8) Taber, D. F.; Amedio, J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618.

(9) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

(10) (a) Wenkert, E.; Michelotti, E. L.; Swindell, C. S.; Tingoli, M. *J. Org. Chem.* **1984**, *49*, 4894. (b) In a minor modification of this process, we significantly reduced the amount of $(dppp)NiCl_2$ catalyst used, with no diminution in yield.

(11) It should be noted that commercial methylmagnesium bromide is less expensive, on a mole basis, than methyl iodide.

(12) (a) Sakai, T.; Nakajima, K.; Sakan, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3683. (b) For an alternative enantioselective approach to such iridoids, see ref 3c above.

(13) Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351.

dissolving metal reduction, to give the corresponding 3-ethylcyclopentanone carboxylates. The absolute stereochemistry deduced for **14**, by using this approach, was confirmed by the conversion of **14** to (+)-isoneonepetalactone (**26**).

While these results are preliminary in nature, the stereochemical course of the cyclization, and the better yields with the cis olefin, can be rationalized (Scheme IV) in the Pd series. It is likely that the ester exists in the extended conformation and that the naphthalene ring lies close to one face of the ester. We assume that the carbonyls are syn,[17] as shown. As the olefin approaches one face of the metallocarbene to form an intermediate metallocyclobutane, the transition metal, with its ligands, will be pushed out from the opposite face. It would thus be reasonable for the olefin to preferentially approach the *more hindered* face of the metallocarbene, fitting into the cleft between the naphthalene ring and the β-keto ester. It is also apparent, on inspection of molecular models, that the cis olefin will fit into this cleft more readily than will the trans olefin.

Synthesis of (+)-Isoneonepetalactone. To confirm the relative and absolute stereochemistry of this intramolecular cyclopropanation, we converted the major (enantiomerically pure) diastereomer **14** from cyclization of the cis olefin to enantiomerically pure (+)-isoneonepetalactone (**26**, Scheme V), a constituent of the essential oil of *Actinidia polygama*.[12] This synthesis was carried through first in the racemic series, starting with racemic cyclopropane **8**.

Opening of the activated cyclopropane **8** with lithium divinylcuprate[18] proceeds smoothly (Scheme V). Routine functional group transformation gives **25**, which on exposure to BBr_3[19] cyclizes to **26**. Racemic isoneonepetalactone so prepared is identical (IR, ^1H NMR) with natural material. It is also clearly distinguishable from the diastereomeric neonepetalactone,[12a] confirming that cyclopropanation proceeds with retention of alkene geometry and that the conjugate addition proceeds with inversion.

For the enantiomerically pure series, β-keto ester **8** was prepared from **14**, by saponification, to recover R*OH **1**, followed by treatment with diazomethane. The same series of reactions (Scheme V) then gave enantiomerically pure isoneonepetalactone (**26**). The synthetic material showed a rotation of +55° (lit.[12a] rotation −66° for the enantiomer[20]), confirming the absolute stereochemistry of **14**.

Conclusion. This report is preliminary in nature. It is clear that both the catalytic metal *and* its associated ligands are associated with the intermediate carbenoid in the product-determining step. As our understanding of the transition state leading to cyclopropanation improves, it should be possible to design more effectively directing chiral esters. Alternatively, it may well be possible to design chiral ligands for the transition metal. Investigations in this direction, as well as the extension of this work to the construction of six-membered rings, are currently under way.

Experimental Section

General. ^1H and ^{13}C NMR spectra were obtained on a Bruker WM-250 spectrometer as solutions in $CDCl_3$. Carbon signals were assigned by an INEPT pulse sequence, u = methylene or quaternary, d = methyl or methine. IR spectra were determined by using CCl_4 solutions. Rotations were measured on a Rudolph Research Autopol III polarimeter. Unless otherwise specified, samples for determination of optical rotation were purified by column chromatography, followed by bulb-to-bulb distillation. Substances for which CH analyses are not reported were purified as specified and gave spectroscopic data consistent with being >95% the assigned structure. Organic chemicals were purchased from Aldrich Chemical Co. The extraction solvent used was a mixture of recovered organic solvents, including methylene chloride, ethyl acetate, and petroleum ether. THF and Et_2O were distilled from sodium metal/benzophenone. The solvent mixtures used for chromatography are volume/volume mixtures. R_f values indicated refer to thin-layer chromatography on Analtech 2.5 × 10 cm, 250-μM analytical plates coated with silica gel GF. Column chromatography was carried out with TLC-mesh silica gel, by following the procedure we have described.[13] Unless otherwise specified, all reactions were carried out in flame-dried glassware under an atmosphere of N_2.

(*E*)-Methyl 3-Hydroxy-6-octenoate (2). Oxidation of (*E*)-4-hexen-1-ol (Aldrich) was effected by the method of Swern.[21] Thus, a solution of oxalyl chloride (20.9 g, 165 mmol, 1.1 equiv) in CH_2Cl_2 (240 mL) was stirred mechanically and cooled to −60 °C in a dry ice/acetone bath. Dimethyl sulfoxide (26 g, 333 mmol, 2.2 equiv) in CH_2Cl_2 (50 mL) was added dropwise. After 30 min, a solution of (*E*)-4-hexen-1-ol (15 g, 150 mmol) in CH_2Cl_2 (120 mL) was added dropwise. After 1 h, triethylamine (96.5 mL, 690 mmol, 4.6 equiv) was added dropwise. The solution was warmed to room temperature and diluted with distilled H_2O (100 mL). The organic layer was washed with 5% aqueous HCl (100 mL) and saturated aqueous $NaHCO_3$ (100 mL), dried (Na_2SO_4), and filtered. Concentration (fractional distillation, atmospheric pressure, Vigreux column) then gave the crude aldehyde as a residual oil (about 15 g; STENCH!).

Methyl acetate (17 g, 229.5 mmol, 1.5 equiv) in THF (15 mL) was added dropwise to lithium diisopropylamide (from 34.3 mL, 244.9 mmol of diisopropylamine and 102 mL of *n*-butyllithium, 2.4 M in hexane, 244.9 mmol) in 208 mL of THF at −78 °C. After 15 min, the crude aldehyde from above, in 15 mL of THF, was added rapidly, while the internal temperature was kept at −78 °C. The reaction mixture was warmed to room temperature, quenched with 10% aqueous HCl, extracted with ethyl acetate (3 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residual oil was chromatographed on 100 g of silica gel with pure petroleum ether, to give **2** as a clear yellow oil (20 g, 76% based on starting alcohol): R_f (20% EtOAc/hexane) 0.27; ^1H NMR δ 1.54–1.6 (m, 2 H), 1.63 (d, J = 4.4 Hz, 3 H), 2.03–2.1 (m, 2 H), 2.4 (m, 2 H), 3.1 (br s, 1 H), 3.7 (s, 3 H), 4.0 (m, 1 H), 5.43 (m, 2 H); ^{13}C NMR δ 172.2 (u), 130.1 (d), 124.4 (d), 66.7 (d), 50.7 (d), 41.0 (u), 39.9 (u), 27.9 (u), 17.0 (d); IR 3600, 2990, 1730, 1610, 1450, 1410, 1385, 1260 cm^{-1}; MS 173 (M + H^+) (28), 155 (85), 141 (16), 123 (100), 103 (11), 101 (30), 99 (86).

(*E*)-Methyl 3-Oxo-6-octenoate (3). Alcohol **2** (20 g, 118 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a slurry of pyridinium chlorochromate[22] (101.7 g, 472 mmol, 4 equiv), anhydrous sodium acetate (40.7 g, 496 mmol, 4.2 equiv), and Florisil (30 g), previously ground together. After 1 h, the mixture was filtered, the residual solid was rinsed with Et_2O (50 mL), EtOAc (50 mL), and CH_2Cl_2 (100 mL), and the organic extract was concentrated. The residue was chromatographed on 50 g of silica gel with pure petroleum ether, to give **3** (15.5 g, 91.2 mmol, 79%) as a clear yellow oil: R_f (20% EtOAc/hexane) 0.54; ^1H NMR δ 1.6 (d, J = 4.5 Hz, 3 H), 2.27 (m, 2 H), 2.6 (t, J = 7.2 Hz, 2 H), 3.5 (s, 2 H), 3.7 (s, 3 H), 5.43 (m, 2 H); ^{13}C NMR δ 201.3 (u), 166.9

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(u), 128.6 (d), 125.2 (d), 51.2 (u), 48.1 (u), 41.9 (u), 25.7 (u), 16.9 (d); IR 3010, 1750, 1720, 1655, 1535, 1450, 1325, 1275, 1040 cm^{-1}; MS 101 (100), 116 (38), 123 (43), 154 (53), 170 (62).

(*Z*)-4-Hexen-1-ol (4). Following a modification of the procedure of Wenkert,[10] we added methylmagnesium bromide[11] (944 mmol, 326 mL of a 2.9 M solution in diethyl ether) all at once to 3.2 g (5.93 mmol) of [1,3-bis(diphenylphosphino)propane]-nickel(II) dichloride. The mixture was warmed to a gentle reflux, and 200 g of dihydropyran (2.38 mol) in 200 mL of toluene was added dropwise. After 24 h at reflux, the reaction mixture was cooled in an ice/water bath, quenched with 0.5 L of aqueous NH_4Cl, and then partitioned between extraction solvent and water. The combined organic layers were dried ($MgSO_4$), concentrated, and distilled bulb-to-bulb [bp_{20} = 75–80 °C (oven)] to give 152.4 g (1.52 mol, 64% yield) of **4** as a clear oil: R_f (20% EtOAc/hexane) 0.25; ^1H NMR δ 1.5–1.8 (m, 5 H) (contains d, 1.6, J = 6.0 Hz), 2.1–2.2 (m, 2 H), 3.6 (t, J = 6.9 Hz, 2 H), 4.3 (br s, 1 H), 5.30–5.55 (m, 2 H); ^{13}C NMR δ 129.7 (d), 124.0 (d), 61.8 (u), 32.2 (u), 22.9 (u), 12.4 (d); IR 3660, 3020, 2950, 1560, 1450, 1380, 1260, 1130 cm^{-1}; MS 100 (9), 82 (59), 67 (100), 57 (36), 55 (58), 41 (71), 39 (53).

(*Z*)-Methyl 3-Hydroxy-6-octenoate (5). Alcohol **4** (30 g, 300 mmol, 0.2 M in CH_2Cl_2), dimethyl sulfoxide[23] (46.9 g, 600 mmol, 2 equiv), and phosphorus pentoxide[24] (76.7 g, 540 mmol, 1.8 equiv) were combined sequentially, with mechanical stirring and external ice/water cooling. The reaction mixture was stirred and warmed to room temperature until disappearance of starting material by TLC (30 min). The flask was immersed again in an ice/water bath, and then triethylamine[25] (106 g, 1050 mmol, 3.5 equiv) was added dropwise over 10 min. After 30 min, the mixture was quenched with 10% aqueous HCl, partitioned between CH_2Cl_2 and saturated aqueous NaCl, and dried ($MgSO_4$). Concentration (atmospheric pressure, Vigreux column) gave the crude aldehyde as a residual oil (ca. 30 g; STENCH!).

Addition of lithium methyl acetate, as for **2**, followed by filtration through silica gel with pure petroleum ether gave 39 g of **5** as a clear yellow oil (74% based on **4**): R_f (20% EtOAc/hexane) 0.27; ^1H NMR δ 5.3–5.6 (m, 6 H), 4.05 (br s, 1 H), 3.6 (s, 3 H), 3.2 (d, J = 3.8 Hz, 1 H), 1.60 (d, J = 6.6 Hz, 3 H), 1.5–2.5 (m, 6 H); ^{13}C NMR δ 12.5 (d), 22.8 (u), 36.1 (u), 41.1 (u), 51.5 (d), 67.4 (d), 124.5 (d), 129.5 (d), 173.0 (u); IR 3600, 2980, 1730, 1560, 1450, 1410, 1380, 1255 cm^{-1}; MS 154 (100), 123 (25), 116 (25), 103 (30).

(*Z*)-Methyl 3-Oxo-6-octenoate (6). Oxidation of **5** (64.5 g, 375 mmol), as for **4**, followed by bulb-to-bulb distillation [bp_{10} = 145 °C (bath)] gave **6** (54 g, 85%) as a colorless oil: R_f (20% EtOAc/hexane) 0.54; ^1H NMR δ 1.62 (d, J = 6.6 Hz, 3 H), 2.3 (q, J = 7.4 Hz, 2 H), 2.6 (t, J = 7.3 Hz, 2 H), 3.5 (s, 2 H), 3.7 (s, 3 H), 5.3–5.5 (m, 2 H); ^{13}C NMR δ 12.6 (d), 20.9 (u), 42.6 (u), 48.9 (u), 52.2 (d), 125.4 (d), 128.0 (d), 167.5 (u), 202.2 (u); IR 3020, 1745, 1715, 1655, 1540, 1450, 1325, 1270, 1050 cm^{-1}; MS 170 (43), 154 (33), 123 (25), 101 (100).

(*Z*)-Methyl 2-Diazo-3-oxo-6-octenoate (7). CH_3CN (200 mL), ketone **6** (22.2 g, 130.6 mmol), methanesulfonyl azide[7] (17.4 g, 143.6 mmol, 1.1 equiv), and triethylamine (26.4 g, 261.2 mmol, 2 equiv) were combined sequentially at room temperature. After 1 h, the mixture was partitioned between 10% aqueous NaOH and extraction solvent, dried (Na_2SO_4), and concentrated. The residual oil was chromatographed on 100 g of silica gel to give **7** as a yellow oil (20.9 g, 82%): R_f (20% EtOAc/hexane) 0.59; ^1H NMR δ 1.6 (d, J = 6.6 Hz, 3 H), 2.7 (q, J = 6.6 Hz, 2 H), 2.9 (t, J = 7.3 Hz, 2 H), 3.8 (s, 3 H), 5.3–5.6 (m, 2 H); ^{13}C NMR δ 12.5 (d), 21.7 (u), 39.8 (u), 51.9 (d), 75.8 (u), 124.9 (d), 128.5 (d), 161.6 (u), 191.9 (u); IR 3090, 2980, 2150, 1720, 1655, 1440, 1320, 1140, 1010 cm^{-1}; MS 196 (19), 138 (71), 136 (100), 113 (73), 108 (79).

Methyl 2-Oxo-6-*endo*-methylbicyclo[3.1.0]hexane-1-carboxylate (8). Ester **7** (20.9 g, 106.6 mmol) in 30 mL of toluene was added dropwise over 5 min to bis(*N*-*tert*-butylsalicylaldiminato)copper(II)[15] (6.5 g, 15.9 mmol) in 50 mL of toluene at 110 °C. After 2.5 h, the mixture was concentrated and then chromatographed on 100 g of silica gel to give a deep yellow oil. This residual oil was distilled bulb-to-bulb [bp_{20} = 110 °C (bath)] to give **8** as a clear pale green oil (14.3 g, 80%): R_f (20% EtOAc/hexane) 0.17; ^1H NMR δ 1.2 (d, J = 7.0 Hz), 1.8–2.7 (m, 6 H), 3.75 (s, 3 H); ^{13}C NMR δ 8.7 (d), 17.0 (u), 29.2 (d), 38.1 (d), 39.3 (u), 42.8 (u), 52.2 (d), 170 (u), 208 (u); IR 3060, 2900, 1750, 1725, 1440, 1320, 1250, 1110, 1040, 960 cm^{-1}; MS 168 (87), 140 (84), 137 (87), 126 (89), 109 (72), 108 (100). For **8** prepared from **13**: $[\alpha]_D$ +45.7° (*c* 0.30, $CHCl_3$). Anal. Calcd for $C_9H_{12}O_3$: C, 64.26; H, 7.19. Found: C, 64.56; H, 7.47.

(3*R*)-1,7,7-Trimethyl-2-(1-naphthyl)bicyclo[2.2.1]hept-3-yl 2-Diazo-3-oxo-6(*Z*)-octenoate (13). Ester **6** (4.5 g, 26.79 mmol, 2.5 equiv), 4-(dimethylamino)pyridine[8] (653 mg, 5.36 mmol, 0.5 equiv), alcohol **1** (3.0 g, 10.71 mmol), and 25 mL of toluene were stirred at 110 °C for 48 h. The reaction mixture was then partitioned between saturated aqueous NH_4Cl and extraction solvent. The combined organic fraction was dried (Na_2SO_4) and concentrated. Excess methyl ester was removed by bulb-to-bulb distillation [bp_{10} = 140–150 °C (bath)] to leave 3.71 g of residue.

This crude β-keto ester, mesyl azide[7] (1.22 g, 10.10 mmol), 10 mL of acetonitrile, and triethylamine (1.85 g, 18.36 mmol) were combined sequentially. After 30 min, the reaction mixture was partitioned between water and extraction solvent, dried (Na_2SO_4), concentrated, and chromatographed on 60 g of silica gel to give **13** (2.4 g, 78%) as a yellow oil, R_f (20% EtOAc/hexane) 0.66. Further elution yielded **1** (1.0 g, 3.57 mmol). For **13**: ^1H NMR δ 0.82–2.46 (m, 9 H), 0.99 (s, 3 H), 1.26 (s, 3 H), 1.28 (s, 3 H), 1.53 (d, J = 7.5 Hz, 3 H), 4.1 (d, J = 8.7 Hz, 1 H), 5.2–5.4 (m, 2 H), 5.6 (d, J = 8.7 Hz, 1 H), 7.3–7.4 (m, 3 H), 7.6 (d, J = 7.3 Hz, 1 H), 7.7 (d, J = 8.1 Hz, 1 H), 8.01 (d, J = 8.4 Hz, 1 H); ^{13}C NMR δ 192.0 (u), 160.5 (u), 135.1 (u), 133.5 (u), 133.0 (u), 129.1 (d), 128.6 (d), 127.0 (2 d), 126.2 (d), 125.3 (d), 124.9 (d), 124.5 (d), 123.3 (d), 80.8 (d), 75.5 (u), 55.6 (d), 51.2 (d), 49.4 (u), 48.5 (u), 42.5 (u), 39.4 (u), 23.9 (u), 21.6 (d), 14.8 (d), 12.9 (d); IR 2990, 2160, 1720, 1665, 1560, 1325, 1210, 1060 cm^{-1}; MS 109 (64), 115 (17), 121 (14), 129 (25), 137 (89), 141 (82), 152 (25), 155 (31), 165 (46), 170 (100), 179 (36), 193 (20), 207 (17), 219 (11), 247 (35), 262 (66), 306 (61), 416 (151) ($M - N_2^+$).

(3*R*)-1,7,7-Trimethyl-2-(1-naphthyl)bicyclo[2.2.1]hept-3-yl 2-Diazo-3-oxo-6(*E*)-octenoate (16). Transesterification[8] was carried out as for the preparation of **13**, starting with 1.52 g (8.94 mmol) of **7**. After workup, excess methyl ester was distilled bulb-to-bulb [bp_{10} = 140–150 °C (bath)] to give 1.27 g of residual oil. Diazo transfer[7] was carried out as for the preparation of **13**, starting with this 1.27 g of crude ester. The residual oil from the diazo transfer was chromatographed on 20 g of silica gel to give **16** (850 mg, 80% based on **1** consumed), as a yellow oil, R_f (20% EtOAc/hexane) 0.66. Further elution yielded recovered **1** (333 mg, 1.19 mmol), R_f (20% EtOAc/hexane) 0.50. For **16**: ^1H NMR δ 0.99 (s, 3 H), 1.26 (s, 3 H), 1.28 (s, 3 H), 1.3–1.9 (m, 7 H), 1.6 (d, J = 4.7 Hz, 3 H), 2.4–2.5 (m, 2 H), 4.1 (d, J = 8.7 Hz, 1 H), 5.2–5.3 (m, 2 H), 5.6 (d, J = 8.7 Hz, 1 H), 7.3–7.4 (m, 3 H), 7.6 (d, J = 7.3 Hz, 1 H), 7.7 (d, J = 8.1 Hz, 1 H), 7.8 (d, J = 7.8 Hz, 1 H), 8.0 (d, J = 8.4 Hz, 1 H); ^{13}C NMR δ 191.6 (u), 160.2 (u), 134.8 (u), 133.3 (u), 132.8 (u), 129.2 (d), 128.8 (d), 126.7 (2 d), 125.9 (d), 125.3 (d), 125.0 (d), 124.2 (d), 123.1 (d), 80.5 (d), 75.1 (u), 55.4 (d), 50.9 (d), 49.1 (u), 48.2 (u), 42.2 (u), 39.3 (u), 26.7 (u), 23.6 (u), 23.5 (d), 21.3 (d), 20.8 (d), 17.6 (d); IR 2995, 2170, 1720, 1665, 1610, 1480, 1400, 1320, 1100 cm^{-1}.

(3*R*)-1,7,7-Trimethyl-2-(1-naphthyl)bicyclo[2.2.1]hept-3-yl 2-Diazo-3-oxo-6-heptenoate (10). Transesterification[8] was carried out as for the preparation of **13**, starting with 1.52 g (9.87 mmol) of methyl 3-oxo-6-octenoate. After workup, the residue was distilled bulb-to-bulb [bp_{10} = 130–140 °C (bath)] to leave 1.10 g of crude bornyl ester. Diazo transfer[7] was carried out as for the preparation of **13**, starting with this crude ester. The residual oil from the diazo transfer was chromatographed as for **13** to give **10** (800 mg, 75% based on **1** consumed), as a yellow oil, R_f (20% EtOAc/hexane) 0.61, and **1** (320 mg, 1.14 mmol). For **10**: ^1H NMR δ 1.0 (s, 3 H), 1.28 (s, 3 H), 1.29 (s, 3 H), 1.3–2.1 (m, 7 H), 2.4–2.5 (m, 2 H), 4.05 (d, J = 8.3 Hz, 1 H), 4.85 (m, 2 H), 5.6 (d, J = 8.4 Hz, 1 H), 5.6–5.7 (m, 1 H), 7.3–7.4 (m, 3 H), 7.6 (d, J = 7.3 Hz, 1 H), 7.7 (d, J = 8.1 Hz, 1 H), 7.8 (d, J = 7.8 Hz, 1 H), 8.02 (d, J = 7.3 Hz, 1 H); ^{13}C NMR δ 191.7 (u), 160.4 (u), 136.8

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(d), 135.1 (u), 133.4 (u), 132.9 (u), 129.0 (d), 126.9 (d), 126.2 (d), 125.2 (d), 124.4 (d), 123.2 (d), 115.1 (u), 80.8 (d), 75.4 (u), 55.6 (d), 51.2 (d), 49.3 (u), 48.4 (u), 42.4 (u), 38.7 (u), 27.9 (u), 23.8 (u), 23.6 (d), 21.6 (d), 14.8 (d); IR 2995, 2135, 1760, 1725, 1660, 1480, 1400, 1330, 1250, 1010 cm^{-1}.

(2*R*,3*R*)-1,7,7-Trimethyl-2-(1-naphthyl)bicyclo[2.2.1]-hept-3-yl (1*S*,5*S*,6*R*)-2-Oxo-6-methylbicyclo[3.1.0]hexane-1-carboxylate (14) and (2*R*,3*R*)-1,7,7-Trimethyl-2-(1-naphthyl)bicyclo[2.2.1]hept-3-yl (1*R*,5*R*,6*S*)-2-Oxo-6-methylbicyclo[3.1.0]hexane-1-carboxylate (15). A solution of **13** (5.0 g, 11.63 mmol) in 15 mL of dry toluene was added dropwise over 10 min to bis(*N*-*tert*-butylsalicylaldiminato)copper(II)[15] (483 mg, 1.163 mmol, 0.1 equiv) in 20 mL of dry toluene at 110 °C. After an additional 10 min, the reaction mixture was concentrated and chromatographed on 100 g of silica gel with 300 mL of petroleum ether, followed sequentially by 300 mL each of 1%, 2%, 3%, 4%, 5%, and 6% EtOAc/petroleum ether. This was followed by 500 mL of 7%, 300 mL of 8%, and 300 mL of 12% EtOAc/petroleum ether. The first 1.8 L was discarded. The next 700 mL was concentrated in vacuo to give **14** (2.9 g, 62%) as a yellow crystalline paste, R_f (20% EtOAc/hexane) 0.33. The next 400 mL was concentrated in vacuo to give **15** (1.5 g, 32%) as a crystalline paste, R_f (20% EtOAc/hexane) 0.24. For **14**: ^1H NMR δ 0.62 (d, J = 6.7 Hz, 3 H), 0.99 (s, 3 H), 1.27 (s, 3 H), 1.31 (s, 3 H), 1.3–1.9 (m, 11 H), 3.9 (d, J = 8.8 Hz, 1 H), 5.5 (d, J = 8.7 Hz, 1 H), 7.3–7.5 (m, 3 H), 7.6 (d, J = 7.4 Hz, 1 H), 7.7 (d, J = 8.0 Hz, 1 H), 7.8 (d, J = 7.0 Hz, 1 H), 7.9 (d, J = 7.2 Hz, 1 H); ^{13}C NMR δ 207.0 (u), 167.6 (u), 136.2 (u), 133.4 (u), 133.2 (u), 128.7 (d), 127.3 (d), 126.3 (d), 126.2 (d), 125.3 (d), 124.6 (d), 123.9 (d), 79.7 (d), 56.1 (d), 51.1 (d), 49.3 (u), 48.5 (u), 42.6 (u), 42.3 (u), 39.2 (u), 37.1 (u), 27.2 (d), 23.9 (d), 21.7 (u), 16.9 (d), 16.7 (d), 14.9 (d), 8.3 (d); IR 2995, 1745, 1730, 1570, 1425, 1270, 1050, 1015, 920 cm^{-1}; MS 416 (8), 306 (30), 262 (15), 177 (10), 165 (12), 137 (100), 121 (23), 109 (10). For **15**: ^1H NMR δ 0.76 (d, J = 6.7 Hz, 3 H), 0.99 (s, 3 H), 1.0–2.05 (m, 11 H), 1.25 (s, 3 H), 1.27 (s, 3 H), 4.0 (d, J = 8.8 Hz, 1 H), 5.5 (d, J = 8.8 Hz, 1 H), 7.3–7.4 (m, 3 H), 7.6 (d, J = 7.3 Hz, 1 H), 7.7 (d, J = 8.1 Hz, 1 H), 7.8 (d, J = 7.0 Hz, 1 H), 7.9 (d, J = 7.6 Hz, 1 H); ^{13}C NMR δ 207.3 (u), 166.9 (u), 135.8 (u), 133.3 (u), 133.1 (u), 128.5 (d), 127.0 (d), 126.4 (d), 126.1 (d), 125.1 (d), 124.4 (d), 123.6 (d), 79.4 (d), 55.5 (d), 50.9 (d), 49.2 (u), 48.3 (u), 42.4 (u), 42.0 (u), 38.0 (u), 35.9 (u), 27.1 (d), 23.8 (d), 21.5 (u), 16.6 (d), 16.5 (d), 14.8 (d), 8.5 (d); IR 2990, 1745, 1725, 1555, 1410, 1270, 1190, 1015 cm^{-1}; MS 416 (8), 306 (35), 262 (19), 247 (11), 179 (12), 170 (35), 165 (18), 141 (25), 137 (100).

(2*R*,3*R*)-1,7,7-Trimethyl-2-(1-naphthyl)bicyclo[2.2.1]-hept-3-yl (1*S*,5*S*,6*S*)-2-Oxo-6-methylbicyclo[3.1.0]hexane-1-carboxylate (17) and (2*R*,3*R*)-1,7,7-Trimethyl-2-(1-naphthyl)bicyclo[2.2.1]hept-3-yl (1*R*,5*R*,6*R*)-2-Oxo-6-methylbicyclo[3.1.0]hexane-1-carboxylate (18). Cyclization was carried out as for **14** and **15** above, starting with 1 g (2.33 mmol) of **16**. The residue after cyclization was chromatographed on 30 g of silica gel with 60 mL of petroleum ether, followed sequentially by 60 mL each of 1%, 2%, 3%, 4%, 5%, and 6% EtOAc/petroleum ether. The column was further eluted with 100 mL of 7%, 60 mL of 8%, and 60 mL of 12% EtOAc/petroleum ether. The first 360 mL was discarded. The next 140 mL was concentrated in vacuo to give **17** (430 mg, 50%) as a yellow crystalline paste, R_f (20% EtOAc/hexane) 0.15. The next 80 mL was concentrated in vacuo to give **18** (379 mg, 40%) as a yellow solid, R_f (20% EtOAc/hexane) 0.23. For **17**: ^1H NMR δ 0.65 (d, J = 6.6 Hz, 2 H), 1.02 (s, 3 H), 1.29 (s, 3 H), 1.4–1.8 (m, 10 H), 4.03 (d, J = 8.8 Hz, 1 H), 5.6 (d, J = 8.8 Hz, 1 H), 7.3–7.4 (m, 3 H), 7.6 (d, J = 7.3 Hz, 1 H), 7.7 (d, J = 8.0 Hz, 1 H), 7.8 (d, J = 7.8 Hz, 1 H), 8.0 (d, J = 8.3 Hz, 1 H); ^{13}C NMR δ 207.0 (u), 165.4 (u), 135.7 (u), 133.5 (u), 133.3 (u), 128.7 (d), 127.3 (d), 126.4 (d), 125.9 (d), 125.1 (d), 124.4 (d), 123.6 (d), 80.2 (d), 55.4 (d), 51.0 (d), 49.4 (u), 48.3 (u), 43.7 (u), 42.5 (u), 35.2 (d), 33.2 (u), 28.0 (u), 24.3 (d), 23.7 (u), 21.6 (d), 21.0 (d), 14.7 (d), 11.6; IR 3000, 1740, 1735, 1580, 1260, 1400 cm^{-1}. For **18**: ^1H NMR δ 0.66 (d, J = 6.6 Hz, 2 H), 1.0 (s, 3 H), 1.28 (s, 3 H), 1.31 (s, 3 H), 1.4–1.9 (m, 10 H), 4.05 (d, J = 8.8 Hz, 1 H), 5.6 (d, J = 8.8 Hz, 1 H), 7.3–7.4 (m, 3 H), 7.6 (d, J = 7.3 Hz, 1 H), 7.7 (d, J = 8.0 Hz, 1 H), 7.8 (d, J = 7.8 Hz, 1 H), 8.0 (d, J = 8.3 Hz, 1 H); ^{13}C NMR δ 206.2 (u), 166.9 (u), 135.8 (u), 133.1 (u), 128.6 (d), 127.3 (d), 126.4 (d), 126.1 (d), 125.1 (d), 124.5 (d), 123.8 (d), 80.6 (d), 55.6 (d), 51.5 (d), 49.4 (u), 48.3 (u), 43.7 (u), 42.5 (u), 34.3 (u), 33.7 (u), 28.7 (u), 24.2 (d), 24.1 (u), 21.5 (d), 20.5 (d), 14.8 (d), 11.8 (d); IR 2995, 1770, 1730, 1580, 1395, 1255 cm^{-1}.

(2*R*,3*R*)-1,7,7-Trimethyl-2-(1-naphthyl)bicyclo[2.2.1]-hept-3-yl (1*S*,5*S*)-2-Oxobicyclo[3.1.0]hexane-1-carboxylate (11) and (2*R*,3*R*)-1,7,7-Trimethyl-2-(1-naphthyl)bicyclo-[2.2.1]hept-3-yl (1*R*,5*R*)-2-Oxobicyclo[3.1.0]hexane-1-carboxylate (12). Cyclization and chromatography were carried out as for **14** and **15**, starting with 1 g (2.33 mmol) of **10**. **11** (580 mg, 62%) was obtained as a yellow crystalline paste, R_f (20% EtOAc/hexane) 0.24. **12** was obtained (300 mg, 32%) as a crystalline paste, R_f (20% EtOAc/hexane) 0.16. For **11**: ^1H NMR δ 0.65 (d, J = 6.6 Hz, 2 H), 1.02 (s, 3 H), 1.29 (s, 3 H), 1.31 (s, 3 H), 1.4–1.8 (m, 10 H), 4.0 (d, J = 8.8 Hz, 1 H), 5.6 (d, J = 8.8 Hz, 1 H), 7.3–7.4 (m, 3 H), 7.6 (d, J = 7.3 Hz, 1 H), 7.7 (d, J = 8.0 Hz, 1 H), 7.8 (d, J = 7.8 Hz, 1 H), 8.0 (d, J = 8.3 Hz, 1 H); ^{13}C NMR δ 206.3 (u), 166.8 (u), 135.8 (u), 133.4 (u), 133.1 (u), 128.7 (d), 127.2 (d), 126.3 (d), 126.1 (d), 125.5 (d), 124.5 (d), 123.6 (d), 79.7 (d), 55.8 (d), 51.0 (d), 49.3 (u), 48.4 (u), 42.6 (u), 36.9 (u), 33.3 (u), 31.7 (d), 23.9 (2 d), 21.7 (u), 20.6 (u), 20.5 (u), 14.8 (d); IR 3000, 1740, 1735, 1580, 1400, 1260 cm^{-1}. For **12**: ^1H NMR δ 0.66 (d, J = 6.6 Hz, 2 H), 1.0 (s, 3 H), 1.28 (s, 3 H), 1.31 (s, 3 H), 1.4–1.9 (m, 10 H), 4.1 (d, J = 8.8 Hz, 1 H), 5.6 (d, J = 8.8 Hz, 1 H), 7.3–7.4 (m, 3 H), 7.6 (d, J = 7.3 Hz, 1 H), 7.7 (d, J = 8.0 Hz, 1 H), 7.8 (d, J = 7.8 Hz, 1 H), 8.0 (d, J = 8.3 Hz, 1 H); IR 2995, 1740, 1730, 1580, 1255, 1395 cm^{-1}.

(1*S*,5*S*,6*R*)-Methyl 2-Oxo-6-methylbicyclo[3.1.0]hexane-1-carboxylate [(+)-8]. Ester **14** (1.5 g, 3.61 mmol), LiOH (16 mL of a 2.24 M solution in water, 36.1 mmol, 10 equiv), and 20 mL of 1,2-dimethoxyethane were heated at 70 °C for 24 h. The reaction mixture was diluted with 30 mL of saturated aqueous NaCl, acidified with 10% aqueous HCl, and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated.

Diazomethane (0.38 N in ether) was added to this crude acid in 10 mL of dry ether until no further N_2 evolution was observed. The crude reaction mixture was concentrated and chromatographed on 50 g of silica gel to give 1 (837 mg, 84%) and 8 (306 mg, 50%). For characterization, see the preparation of racemic **8** above.

(3*S*)-2-(Methoxycarbonyl)-3-but-1-en-3(*R*)-ylcyclopentanone (19). Tetravinyltin[18] (19.6 g, 73.35 mmol, 2.37 equiv), 150 mL of ether, and low halide CH_3Li (152.7 mL of a 1.7 M solution in diethyl ether, 259.7 mmol, 8.39 equiv) were combined sequentially. After 1 h, the flask was immersed in a −40 °C bath and copper(I) bromide–dimethyl sulfide complex (27.8 g, 135.25 mmol, 4.37 equiv) dissolved in dimethyl sulfide (100 mL) was added via syringe. After 30 min at −40 °C and 30 min at −20 °C, ester **8** (5.2 g, 30.95 mmol) in Et_2O (10 mL) was added via syringe over 12 min. After 1 h at −20 °C and 1 h at 0 °C, the reaction mixture was partitioned between 10% aqueous HCl and ethyl acetate, dried (Na_2SO_4), and concentrated. The residual oil was chromatographed on 50 g of silica gel to give **19** (4.0 g, 76%) as a clear oil and unreacted **8** (700 mg). For **19**: R_f (20% EtOAc/hexane) 0.51; ^1H NMR δ 1.05 (d, J = 6.7 Hz, 3 H), 1.4–1.7 (m, 1 H), 2.1–2.65 (m, 5 H), 2.95 (d, J = 12.1 Hz, 1 H), 3.75 (s, 3 H), 4.9–5.1 (m, 2 H), 5.55–5.75 (m, 1 H); ^{13}C NMR δ 17.8 (d), 25.3 (u), 38.5 (u), 43.5 (d), 46.2 (d), 52.3 (d), 60.3 (d), 114.6 (u), 141.5 (d), 170.1 (u), 211.8 (u); IR 3080, 2980, 1752, 1720, 1640, 1410, 1280, 1120, 920 cm^{-1}; MS 196 (8), 165 (19), 149 (13), 141 (100), 113 (41), 109 (98); $[\alpha]_D$ −52.5° (*c* 0.122, $CHCl_3$). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.25; H, 8.41.

(7*S*)-Methyl 7-But-1-en-3(*R*)-yl-2,5-dioxaspiro[4.4]nonane-6-carboxylate (20). Ketone **19** (1.5 g, 7.96 mmol), ethylene glycol (16.3 mL, 292.1 mmol, 36 equiv), 10 mL of methylene chloride, and $BF_3{\cdot}Et_2O$[26] (5.2 mL, 42.4 mmol, 5.33 equiv) were combined sequentially. After 24 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then partitioned between saturated aqueous NaCl and CH_2Cl_2. The organic extract was dried (Na_2SO_4) and concentrated. The residual oil was chromatographed on 20 g of silica gel to give 1.54 g (86%) of **20** as a colorless oil: R_f (20% EtOAc/hexane) 0.47; ^1H NMR δ 1.0 (d, J = 6.8 Hz, 3 H), 1.2–1.5 (m, 1 H), 1.75–2.35 (m, 5 H), 2.65 (d, J = 12.0 Hz, 1 H), 3.73 (s, 3 H), 3.8–4.1 (m, 4 H), 4.85–5.10 (m, 1 H); ^{13}C NMR δ 18.2 (d), 27.3 (u), 37.0 (u), 43.8 (d), 46.4 (d),

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51.7 (d), 57.8 (d), 64.1 (u), 65.2 (u), 113.9 (u), 117.6 (u), 143.7 (d), 172.9 (u); IR 2990, 1745, 1560, 1440, 1380, 1260, 1150, 1090, 950 cm^{-1}; MS 240 (3), 185 (100), 153 (42), 141 (22), 113 (27), 109 (47), 100 (34); $[\alpha]_D$ −34.3° (*c* 0.928, $CHCl_3$).

(7*S*)-Methyl 7-(1-Hydroxyprop-2(*R*)-yl)-2,5-dioxaspiro-[4.4]nonane-6-carboxylate (21). A gas bubbler was charged with **20** (100 mg, 0.416 mmol), CH_2Cl_2/CH_3OH solution (5 mL, 1:2 by volume), and a crystal of Sudan III.[27] Ozone was then bubbled through the solution at −78 °C until the red color disappeared. After being purged with N_2, the reaction mixture was transferred to a round-bottomed flask, and sodium borohydride (30 mg, 0.833 mmol, 2 equiv) was added. After 30 min, the reaction mixture was concentrated and chromatographed on 2 g of silica gel to give **21** (94 mg, 93%) as a clear yellow oil: R_f (40% acetone/hexane) 0.37; ^1H NMR δ 0.95 (d, *J* = 6.8 Hz, 3 H), 1.25–2.65 (m, 7 H), 2.75 (d, *J* = 12.1 Hz, 1 H), 3.4–3.5 (m, 2 H), 3.72 (s, 3 H), 3.8–4.2 (m, 4 H); ^{13}C NMR δ 14.8 (d), 27.0 (u), 37.2 (u), 40.6 (d), 43.1 (d), 52.0 (d), 58.0 (d), 64.3 (u), 65.2 (u), 66.6 (u), 117.8 (u), 173.4 (u); IR 2970, 1735, 1560, 1443, 1265, 1150, 1050 cm^{-1}; MS 244 (3), 213 (10), 185 (49), 169 (12), 109 (28), 99 (100); $[\alpha]_D$ −41.1° (*c* 0.648, $CHCl_3$).

(7*S*)-Methyl 7-(1-Methoxyprop-2(*R*)-yl)-2,5-dioxaspiro-[4.4]nonane-6-carboxylate (22). Silver(I) oxide[28] (949 mg, 4.09 mmol, 5.0 equiv), CH_3CN (672 mg, 16.39 mmol, 20 equiv), CH_3I (2.09 g, 14.74 mmol, 18 equiv), and **21** (200 mg, 0.819 mmol) were combined sequentially. After 24 h at 80 °C, the reaction mixture was cooled and filtered with 50 mL of EtOAc. The organic extract was concentrated and chromatographed on 5.0 g of silica gel to give **22** (130 mg, 68%) as a yellow oil, R_f (40% acetone/hexane) 0.59, and recovered **21** (19 mg). For **22**: ^1H NMR δ 0.95 (d, *J* = 6.9 Hz, 3 H), 1.25–2.65 (m, 6 H), 3.1–3.4 (m, 2 H), 2.85 (d, *J* = 12.0 Hz, 1 H), 3.25 (s, 3 H), 3.75 (s, 3 H), 3.9–4.1 (m, 4 H); ^{13}C NMR δ 172.3 (u), 117.8 (u), 77.6 (u), 65.2 (u), 64.1 (u), 60.1 (d), 58.2 (d), 51.3 (d), 44.9 (d), 38.3 (d), 30.8 (u), 20.7 (u), 14.9 (d); IR 2980, 1750, 1460, 1270, 1010 cm^{-1}; MS 259 (18) $(M + H)^+$, 258 (5) (M^+), 227 (100), 225 (18), 195 (82), 99 (33); $[\alpha]_D$ −53.1° (*c* 0.610, $CHCl_3$).

(3*S*)-Methyl 3-(1-Methoxyprop-2(*R*)-yl)-1-oxocyclopentane-2-carboxylate (23). Ketal **22** (358 mg, 1.39 mmol), 1.5 mL of dry acetone, and 180 mg of Dowex-50W ion-exchange resin were combined sequentially. After 48 h at 60 °C, the reaction mixture was cooled and then filtered by using 50 mL of acetone. The organic extract was concentrated and then chromatographed on 10 g of silica gel to give **23** (261 mg, 1.23 mmol, 88%) as a clear oil: R_f (40% acetone/hexane) 0.55; ^1H NMR δ 0.98 (d, *J* = 6.9 Hz, 3 H), 1.4–2.7 (m, 8 H), 3.1 (d, *J* = 12.1 Hz, 1 H), 3.25 (s, 3 H), 3.75 (s, 3 H); ^{13}C NMR δ 212.0 (u), 169.9 (u), 77.0 (u), 60.3 (d), 58.4 (d), 52.3 (d), 44.3 (d), 38.1 (d), 38.0 (u), 25.3 (u), 14.5 (d); IR 2990, 2900, 1765, 1740, 1560, 1445, 1270, 1020 cm^{-1}; MS 214 (2), 182 (17), 151 (14), 141 (95), 127 (20), 113 (11), 109 (100); $[\alpha]_D$ −70.7° (*c* 0.315, $CHCl_3$).

(3*S*)-Methyl 3-(1-Methoxyprop-2(*R*)-yl)-1-[(diethoxyphosphoryl)oxy]cyclopent-1-ene-2-carboxylate (24). Sodium hydride (48.0 g of a 50% oil dispersion, 0.992 mmol, 1.1 equiv), 1 mL of ether, and ester **23** (193 mg, 0.902 mmol) in 1 mL of ether were combined sequentially at 0 °C. After 30 min, diethyl chlorophosphate[29] (171.2 mg, 0.992 mmol, 1.1 equiv) was added all at once. After 30 min, the reaction mixture was partitioned between extraction solvent and aqueous NH_4Cl. The combined organic extracts were dried (Na_2SO_4), concentrated, and distilled bulb-to-bulb [bp_{10} = 70–75 °C (bath)] to remove excess diethyl chlorophosphate. The residue was chromatographed on 3 g of silica gel to give **24** (238 mg, 75%) as a clear yellow oil: R_f (40% acetone/hexane) 0.39; ^1H NMR δ 0.76 (d, *J* = 6.9 Hz, 3 H), 1.2–1.4 (t, *J* = 8.0 Hz, 6 H), 1.65–2.05 (m, 2 H), 2.3–2.4 (m, 1 H), 2.7–2.8 (m, 2 H), 3.1–3.2 (m, 3 H), 3.3 (s, 3 H), 3.7 (s, 3 H), 4.2–4.3 (m, 4 H); ^{13}C NMR δ 11.4 (d), 16.0 (d), 16.1 (d), 20.2 (u), 32.8 (u), 34.4 (d), 42.7 (d), 51.1 (d), 58.6 (d), 64.9 (u), 64.8 (u), 76.9 (u), 116.3 (u), 158.1 (u), 164.1 (u); MS 350 (16), 318 (36), 286 (54), 277 (24), 258 (13), 245 (100), 217 (66), 189 (74), 161 (21), 109 (53); $[\alpha]_D$ +11.3° (*c* 0.67, $CHCl_3$).

(3*S*)-Methyl 3-(1-Methoxyprop-2(*R*)-yl)-1-methylcyclopent-1-ene-2-carboxylate (25). Copper(I) iodide[30] (244 mg, 1.18 mmol, 4 equiv), ether (10 mL), and low halide CH_3Li (1.38 mL of a 1.7 M solution in ether, 2.35 mmol, 8 equiv) were combined sequentially at 0 °C. After 15 min, the reaction flask was transferred to a dry ice/acetone bath. After 30 min, enol phosphate **24** (103 mg, 0.294 mmol) of 1 mL of Et_2O was added dropwise via syringe. After 1 h at −78 °C and 1.5 h at −50 °C, the reaction mixture was warmed to −20 °C and then partitioned between aqueous NH_4Cl and ether. The organic extract was dried (Na_2SO_4), concentrated, and then chromatographed on 3 g of silica gel to give **25** (32 mg, 61%) as a clear oil, R_f (40% acetone/hexane) 0.69, and recovered **24** (16 mg, 0.046 mmol). For **25**: ^1H NMR δ 0.70 (d, *J* = 6.9 Hz, 3 H), 2.1 (s, 3 H), 1.6–2.5 (m, 6 H), 3.2–3.3 (m, 2 H), 3.3 (s, 3 H), 3.7 (s, 3 H); ^{13}C NMR δ 166.7 (u), 156.0 (u), 129.4 (u), 77.5 (u), 58.6 (d), 50.8 (d), 47.3 (d), 39.9 (u), 34.5 (d), 22.2 (u), 16.4 (d), 11.3 (d); IR 2950, 1714, 1436, 1220, 1114 cm^{-1}; $[\alpha]_D$ +13.3° (*c* 0.40, $CHCl_3$).

(+)-Isoneonepetalactone (26). Ester **25** (152 mg, 0.717 mmol), 1 mL of dry CH_2Cl_2, 15-crown-5 [14.3 mL of 0.3 M solution (6 equiv) saturated with NaI in CH_2Cl_2], and BBr_3[19] (2.15 mL of a 1 M solution in CH_2Cl_2, 2.15 mmol, 3 equiv) were combined sequentially at −23 °C (dry ice/CCl_4 bath). After 5 min, the reaction mixture was warmed to room temperature and concentrated. The residue was chromatographed on 5 g of silica gel to give **26** (70 mg, 49%) as a clear oil: R_f (40% acetone/hexane) 0.51; ^1H NMR δ 0.94 (d, *J* = 6.6 Hz, 3 H), 1.4–1.5 (m, 2 H), 1.7–1.85 (m, 1 H), 2.2 (t, *J* = 8.0 Hz, 3 H), 2.3–2.6 (m, 3 H), 3.89, 4.25 (each 1 H, AB q of ABX, J_{AX} = 11.2 Hz, J_{BX} = 5 Hz, J_{AB} = 11.2 Hz); this ^1H NMR data is consistent with that reported[12] and *not* consistent with the diastereomeric neonepetalactone; ^{13}C NMR δ 164.1 (u), 160.3 (u), 124.4 (u), 74.9 (u), 50.3 (d), 38.6 (u), 36.1 (d), 29.3 (u), 16.5 (d), 14.1 (d); IR 2963, 1721, 1645 cm^{-1}; MS 166 (M^+) (74), 151 (22), 136 (10), 124 (75), 121 (36), 107 (27), 105 (11), 93 (60), 79 (100), 77 (38), 53 (21). In the enantiomerically pure series, $[\alpha]_D$ +55.0° (*c* 0.55, $CHCl_3$) (11-mg sample, *chromatographed only*!).

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Registry No. 1, 86835-18-9; (±)-2, 114249-95-5; 3, 62344-14-3; 4, 928-91-6; (*E*)-4, 928-92-7; 4 (aldehyde), 4634-89-3; (*E*)-4 (aldehyde), 25166-87-4; (±)-5, 114273-18-6; 6, 22617-63-6; 7, 62344-21-2; 8, 114375-03-0; 8 (acid), 114250-08-7; 10, 114249-96-6; 10 (dione), 110971-06-7; 11, 114249-97-7; 12, 114298-59-8; 13, 114249-98-8; 13 (dione), 114250-07-6; 14, 114249-99-9; 15, 114298-60-1; 16, 114298-61-2; 16 (dione), 114298-65-6; 17, 114298-62-3; 18, 114298-63-4; 19, 114250-00-9; 20, 114250-01-0; 21, 114250-02-1; 22, 114250-03-2; 23, 114250-04-3; 24, 114250-05-4; 25, 114250-06-5; 26, 114298-64-5; $CH_3CO_2CH_3$, 79-20-9; $CH_3OCOCH_2CO(CH_2)_2CH{=}CH_2$, 30414-57-4.

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