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# Synthesis of (+)-Coronafacic Acid

Douglass F. Taber,* Ritesh B. Sheth, and Weiwei Tian

*Department of Chemistry & Biochemistry, University of Delaware, Newark, Delaware 19716*

*taberdf@udel.edu*

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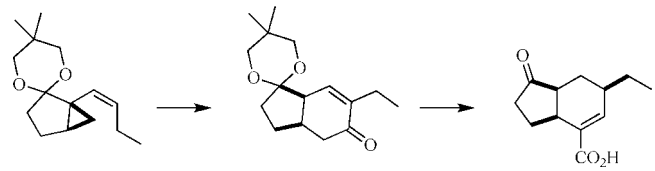
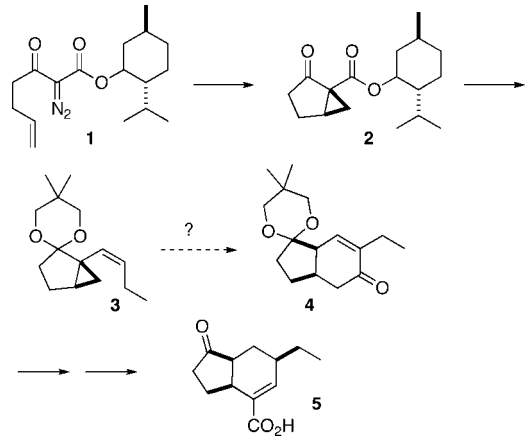


An enantioselective synthesis of (+)-coronafacic acid has been achieved. Rhodium-catalyzed cyclization of an α-diazoester provided the intermediate cyclopentanone in high enantiomeric purity. Subsequent Fe-mediated cyclocarbonylation of a derived alkenyl cyclopropane gave a bicyclic enone that then was hydrogenated and carried on to the natural product.

## Introduction

Bicyclic and polycyclic ring systems are common in structurally complex and physiologically active natural products. Although there are many methods of preparing such ring systems, the number of approaches to *carbopolycyclic* scaffolds is more limited. Corey demonstrated the utility of an enzyme to convert 20,21-dehydro-2,3-oxidosqualene to a dehydroprotosterol. Hajos[2] employed a catalytic amount of (*S*)-(−)-proline in an asymmetric aldol condensation to form optically pure bicyclic intermediates. We[3] were able to demonstrate that a single stereogenic center on the bridge between the diene and dienophile could set the absolute center of an intramolecular Diels−Alder reaction leading to a carbobicyclic 6,6-system. Corey[4] reported examples of catalytic enantioselective [2 + 2] cycloaddition catalyzed by chiral aluminum bromide complexes to form 5,4-, 6,4-, and 7,4-carbobicyclic systems. We[5] also reported another approach to enantioselective polycyclic construction, utilizing Shi epoxidation followed by selective ring opening, and then intramolecular alkylation to set the stereogenic centers. We[6] further showed in our synthesis of (+)-sulcatine G that enantiospecific C−H insertion, followed by intramolecular alkylation, could also be applied to carbobicycle construction. Schaus[7]demonstrated the utility of the Morita−Baylis−Hillman reaction, coupled with the Hosomi−Sakauri reacton, to construct 6,6-bicyclic systems. Gaunt[8] reported a strategy using oxidative dearomatization and amine-catalyzed enantioselective desymmetrizing Michael reaction to form 6,6-carbobicycles. In the Phillips[9] synthesis of (+)-cyanthiwigin U, tandem metathesis was used to enantioselectively construct the polycarbocycle. Recently, Ishihara[10] utilized enantioselective Robinson annulation and cycloaddition reactions catalyzed by chiral Lewis acids for polycarbocycle construction.

**SCHEME 1**



We had developed (Scheme 1) a general route to enantiomerically pure 5,3- and 6,3-carbobicyclic scaffolds by cyclization of menthyl esters such as **1** to the cyclopentanone **2**.[11a] Nakada[11l,r,s] later reported an enantioselective preparation of similar carbocyclic esters and sulfones by copper-catalyzed

(1) Corey, E. J.; Lin, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1969**, *91*, 2132.
(2) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.
(3) Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992.
(4) Corey, E. J.; Canales, E. *J. Am. Chem. Soc.* **2007**, *129*, 12686.
(5) Taber, D. F.; He, T.; Xu, M. *J. Am. Chem. Soc.* **2004**, *126*, 13900.
(6) Taber, D. F.; Frankowski, K. J. *J. Org. Chem.* **2005**, *70*, 6417.
(7) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334.
(8) Rodgen, S. A.; Schaus, S. E. *Angew Chem., Int Ed.* **2006**, *45*, 4929.
(9) Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. I. *J. Am. Chem. Soc.* **2008**, *130*, 404.
(10) Ishihara, K.; Fushimi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7532.

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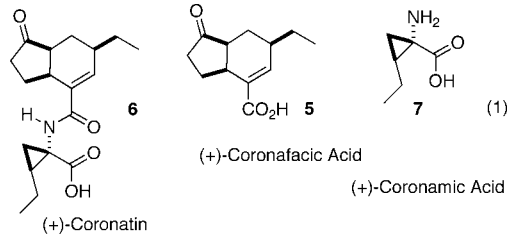
asymmetric intramolecular cyclopropanation. We have improved upon our intramolecular cyclization[11a] by increasing the selectivity and preparative yield of the cyclization. We anticipated that we could convert the ester to the alkenyl cyclopropane **3**. We speculated[12] that Fe-mediated cyclocarbonylation of the alkenyl cyclopropane could deliver the bicyclic enone **4**. If this were successful, the enone **4** could then be transformed in a few steps to the natural product (+)-coronafacic acid **5**.

## Background and Results

Coronatin **6** (eq 1) is a phytotoxin produced by *Pseudomonas syringae*. Its structure is composed of coronafacic acid **5**, a bicyclic core with three stereogenic centers, and coronamic acid **7**, a cyclopropane amino acid derived from isoleucine. Both coronatin and coronafacic acid have been reported to mimic jasmonic acid. All three compounds induce tubers, induce cell expansion, inhibit cell division, and promote senescence in plants.[13] While there were 15 previous total syntheses of coronafacic acid,[14] only one enantioselective route had been reported.[14m]




**Intramolecular Cyclopropanation.** Dirhodium tetracarboxylate catalysts are known to cyclize α-diazo esters, such as **1**. We had previously cyclized **1** to a 1:1 mixture of **2** and **8** (eq 2) using a copper bronze catalyst.[11a] We separated the menthyl esters **2** and **8** by column chromatography, leading to pure **2** in 21% yield. We have investigated a diverse selection of dirhodium tetracarboxylate catalysts to improve upon those earlier results.

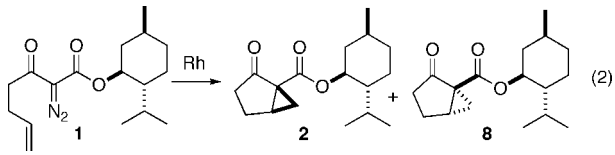
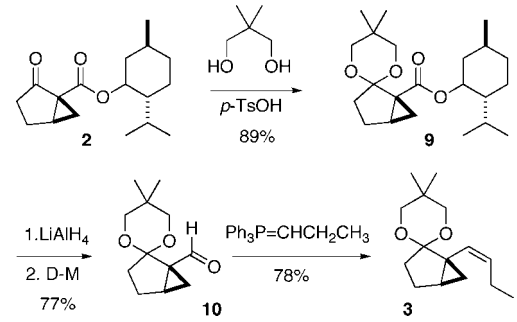



**TABLE 1. Cyclization of Diazo Menthyl Ester 1**

| entry | rhodium ligand | solvent | *T* (°C) | diastereoselectivity (**2**:**8**) | yield[a] (%) |
|---|---|---|---|---|---|
| 1 | piv[b] | $CH_2Cl_2$ | 25 | 2.5:1 | 95 |
| 2 | piv[b] | $PhCH_3$ | 25 | 1.5:1 | 91 |
| 3 | piv[b] | $C_6H_{12}$ | 25 | 1.2:1 | 80 |
| 4 | piv[b] | $CCl_4$ | 25 | 1.2:1 | 70 |
| 5 | piv[b] | $CH_2Cl_2$ | −78 | 3.0:1 | 90 |
| 6 | tfa[c] | $CH_2Cl_2$ | 25 | 0.9:1 | 70 |
| 7 | octd | $CH_2Cl_2$ | 25 | 1.2:1 | 89 |
| 8 | $Ph_3CCO_2$[e] | $CH_2Cl_2$ | 25 | 0.7:1 | 75 |
| 9 | OAc[f] | $CH_2Cl_2$ | 25 | 1.0:1 | 80 |
| 10 | Esp[g] | $CH_2Cl_2$ | 25 | 1.3:1 | 88 |
| 11 | *R*-ptpah | $CH_2Cl_2$ | 25 | 1.7:1 | 71 |
| 12 | *R*-pttl[i] | $CH_2Cl_2$ | 25 | 1.3:1 | 82 |
| 13 | *S*-dosp[j] | $CH_2Cl_2$ | 25 | 1.7:1 | 91 |
| 14 | *S*-tbsp[k] | $CH_2Cl_2$ | 25 | 1.5:1 | 89 |

[a] Yields reported are for the isolated mixture of the two diastereomers. [b] See ref 15a. [c] See ref 15b. [d] See ref 15c. [e] See ref 15d. [f] See ref 15e. [g] See ref 15f. [h] See ref 15g. [i] See ref 15h. [j] See ref 15i. [k] See ref 15j.

**SCHEME 2**




We have found (Table 1) that, by using Rh(II) catalysts, we could induce some diastereoselectivity in this cyclization. We found that dirhodium pivalate at room temperature provided the best preparative yield, 63%, of the desired cyclopentanone **2**.

**Preparation of Alkenyl Cyclopropane 6.** With the initial two stereocenters set, we protected (Scheme 2) the ketone as the ketal **9**. Attempts to reduce the ester directly to the aldehyde with less than 1 equiv of lithium aluminum hydride or with DIBAL delivered a mixture of alcohol, aldehyde, and the starting ester. We found that completely converting the ester **2** to the alcohol followed by oxidization to aldehyde **10** with Dess−Martin

(11) For previous preparations of cyclohexanones and cyclopentanones via intramolecular cyclopropanation, see: (a) Taber, D. F.; Saleh, S. A.; Korsmeyer, R. W. *J. Org. Chem.* **1980**, *45*, 4699. (b) Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **1998**, *63*, 3717. (c) Dauben, W. G.; Hendricks, R. T.; Luzzio, M. J.; Ng, H. P. *Tetrahedron Lett.* **1990**, *31*, 6969. (d) Pique, C.; Fahndrich, B.; Pfaltz, A *Synlett* **1995**, 491. Special Issue: (e) Park, S.-W.; Son, J.-H.; Kim, S.-G.; Ahn, K. H. *Tetrahedron: Asymmetry* **1999**, *10*, 1903. (f) Kim, S. G.; Cho, C. W.; Ahn, K. H. *Tetrahedron* **1999**, *55*, 10079. (g) Barberis, M.; Estevan, F.; Lahuerta, P.; Perez-Prieto, J.; Sanau, M. *Inorg. Chem.* **2001**, *40*, 4226. (h) Barberis, M.; Prieto, J.; Stiriba, S.-E.; Lahuerta, P. *Org. Lett.* **2001**, *3*, 3317. (i) Saha, B.; Uchida, T.; Katsuki, T. *Chem. Lett.* **2002**, *8*, 846. (j) Barberis, M.; Perez-Prieto, J.; Herbst, K.; Lahuerta, P. *Organometallics* **2002**, *21*, 1667. (k) Saha, B.; Uchida, T.; Katsuki, T. *Tetrahedron: Asymmetry* **2003**, *14*, 823. (l) Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 2860. (m) Honma, M.; Nakada, M. *Tetrahedron Lett.* **2003**, *44*, 9007. (n) Wong, A.; Welch, C. J.; Kuethe, J. T.; Vazquez, E.; Shaimi, M.; Henderson, D.; Davies, I. W.; Hughes, D. L. *Org. Biomol. Chem.* **2004**, *2*, 168. (o) Estevan, F.; Lahuerta, P.; Lloret, J.; Perez-Prieto, J.; Werner, H. *Organometallics* **2004**, *23*, 1369. (p) Estevan, F.; Lahuerta, P.; Lloret, J.; Penno, D.; Sanau, M.; Ubeda, M. A. *J. Organomet. Chem.* **2005**, *690*, 4424. (q) Uchida, T.; Katsuki, T. *Synthesis* **2006**, 1715. (r) Ida, R; Nakada, M. *Tetrahedron Lett.* **2007**, *48*, 4856. (s) Takeda, H.; Honma, M.; Ida, R.; Sawada, T.; Nakada, M. *Synlett* **2007**, *4*, 579.

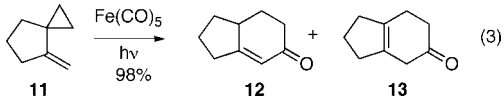
(12) For the development of Fe-mediated cyclocarbonylation, see: (a) Victor, R.; Ben-Shoshan, R.; Sarel, S. *J. Org. Chem.* **1978**, *43*, 4971. (b) Taber, D. F.; Kanai, K.; Jiang, Q.; Bui, G. *J. Am. Chem. Soc.* **2000**, *122*, 6807. (c) Taber, D. F.; Bui, G.; Chen, B. *J. Org. Chem.* **2001**, *66*, 3423. (d) Taber, D. F.; Joshi, P. V.; Kanai, K. *J. Org. Chem.* **2004**, *69*, 2268. (e) Taber, D. F.; Sheth, R. B. *J. Org. Chem.* **2008**, *73*, 8030.

(13) For a recent review of chemistry and biological properties of coronatin and coronafacic acid: Mitchell, R. E. *Chem. N. Z.* **2004**, *68*, 24.

(14) For previous coronafacic acid syntheses, see: (a) Ichihara, A.; Kimura, R.; Moryasu, K.; Sakamura, S. *Tetrahedron Lett.* **1977**, *18*, 4331. (b) Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 2463. (c) Ichihara, A.; Kimura, R.; Moryasu, K.; Sakamura, S. *J. Am. Chem. Soc.* **1980**, *102*, 6353. (d) Tsuji, J. *Pure Appl. Chem.* **1981**, *53*, 2371. (e) Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* **1981**, *22*, 2735. (f) Nakayama, M.; Ohira, S.; Okamura, Y.; Soga, S. *Chem. Lett.* **1981**, 731. (g) Nakayama, M.; Ohira, S. *Agric. Biol. Chem.* **1983**, *47*, 1689. (h) Liu, H. J.; Brunet, M. L *Can. J. Chem.* **1984**, *62*, 1747. (i) Bhamare, N. K.; Granger, T.; Macas, T. S.; Yates, P. *J. Chem. Soc., Chem. Commun.* **1990**, 739. (j) Mehta, G.; Praveen, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1573. (k) Hoelder, S.; Blechert, S. *Synlett* **1996**, 505. (l) Nara, S.; Toshima, H.; Ichihara, A. *Tetrahedron Lett.* **1996**, *37*, 6745. (m) Nara, S.; Toshima, H.; Ichihara, A. *Tetrahedron* **1997**, *53*, 9509. (n) Sono, M.; Hashimoto, A.; Nakashima, K.; Tori, M. *Tetrahedron Lett.* **2000**, *41*, 5115. (o) Mehta, G.; Reddy, D. S. *J. Chem. Soc., Perkin Trans. 1* **2001**, *10*, 1153. (p) Moreau, B.; Ginisty, M.; Alberico, D.; Charette, A. B. *J. Org. Chem.* **2007**, *72*, 1235.

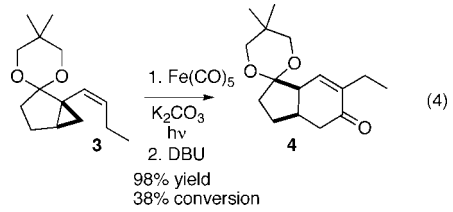
reagent was more effective. We were then able to perform a Wittig reaction on aldehyde **10** to give alkenyl cyclopropane **3**.

**Preparation of Enone 9.** We[12b−d] previously reported the preparation of 2,5- and 5-substituted cyclohexenones via Fe-mediated cyclocarbonylation. More recently, we found that we could couple the Wittig reaction with Fe-mediated cyclocarbonylation to convert aldehydes to 2-substituted cyclohexenones.[12e] Sarel[12a] demonstrated the photochemical expansion of a methylene spiroalkane **11** to the bicyclic enones **12** and **13** in his studies of (+)-α-thujene (eq 3). The cyclocarbonylation to a bicyclic enone from a 5,3- or 6,3-ring fused alkenyl cyclopropane such as **3** had not yet been reported.




(3)

We found (eq 4) that UV irradiation of **3** in the presence of $Fe(CO)_5$ converted the alkenyl cyclopropane **3** to the bicyclic cyclohexenone **4** in low yield with accompanying deketalization. We found that by adding $K_2CO_3$ to the irradiation, the reaction was buffered and ketal deprotection was avoided. The use of tetrahydrofuran, rather than 2-propanol,[12b−e] as the reaction solvent doubled the conversion of **3** to **4**. We found it practical to run the cyclocarbonylation to about 40% conversion (TLC), as longer irradiation led to diminished yield. The unreacted starting material was easily separated and recycled.

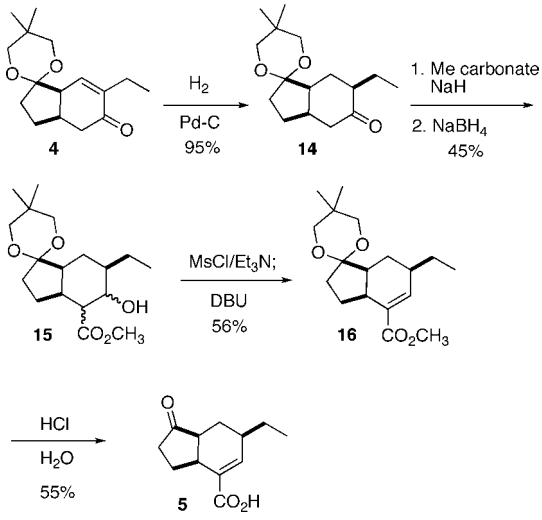



(4)

The kinetic product from the cyclocarbonylation was the $\beta,\gamma$-unsaturated ketone. This was not purified but was converted to the desired $\alpha,\beta$-unsaturated ketone **4** by stirring for 1 h at room temperature with DBU.

**Synthesis of (+)-Coronafacic Acid.** Pd-mediated hydrogenation of the cyclohexenone **4** (Scheme 3) at ambient temperature and pressure provided the bicyclic ketone **11** as a single diastereomer. Carbomethoxylation followed by reduction with sodium borohydride gave the alcohol **12** as a mixture of diastereomers. Dehydration of the mixture by mesylation and subsequent addition of DBU gave the ketal-protected coronafacic methyl ester **13** as a single diastereomer. Deprotection and ester hydrolysis were then completed in one step with aqueous HCl at reflux to give the natural product **5**. The physical data, including optical rotation (obsd $[\alpha]^{20}_D$ +104; lit.[14o] $[\alpha]^{20}_D$ +105), were consistent with those previously reported for (+)-coronafacic acid.

**SCHEME 3**




## Conclusion

We have completed an enantioselective synthesis of (+)-coronofacic acid. We were able to set the initial two stereogenic centers utilizing rhodium-catalyzed intramolecular cyclopropanation. We were then able to expand the cyclopropane utilizing Fe-mediated cyclocarbonylation. We expect that this will be a general route to enantiomerically pure 6,5- and 6,6-carbobicyclic systems.

## Experimental Section

**(1*S*,2*R*,5*S*)-5-Methyl-2-(propan-2-yl)cyclohexyl 2-Oxobicyclo-[3.1.0]hexane-1-carboxylate 2 and 8.** $Rh_2(Piv)_4$[15a] (5 mg) was added to α-diazoester **1**[11a] (6.12 g, 20 mmol) in 20 mL of dry $CH_2Cl_2$ (1.0 M) at rt. The solution was stirred at rt for 1 h, and then additional $Rh_2(Piv)_4$ (5 mg) was added and the reaction allowed to stir for an additional 2 h. The mixture was concentrated and the residue chromatographed using 94:6 hexanes/EtOAc as elution solvent to give the cyclopentanone **2** (3.61 g, 63% yield) and **8** (1.78 g, 32% yield) as an oil. Cyclopentanone **2** was then crystallized at −78 °C in petroleum ether (5 mL) to give **2** (3.49 g, 62% as a white crystalline solid: mp = 34−36 °C; $[\alpha]^{20}_D$ +47.2 (*c* = 1.0, $CH_2Cl_2$); TLC $R_f$ = 0.27 (9:1 hexanes/EtOAc); $^1$H NMR $\delta$ 4.71 (dt, *J* = 4.9, 11.5 Hz, 1H), 2.54 (m, 1H), 2.22 (m, 3H), 2.01 (m, 4H), 1.68 (d, *J* = 12.1 Hz, 2H), 1.34−1.48 (m, 3H), 0.88−1.05 (m, 9H), 0.75 (d, *J* = 7.6 Hz, 3H); $^{13}$C NMR $\delta$ u[16] 207.0, 167.6, 40.6, 37.8, 34.2, 33.5, 21.4, 21.0; d 74.9, 46.8, 32.4, 31.3, 25.8, 23.1, 21.9, 20.8, 16.0; IR 2952, 1736, 1454, 1383, 1311 cm$^{-1}$; MS *m*/*z* 279 (M + H, 100), 263 (48), 141 (98), 123 (79); HRMS calcd for $C_{17}H_{27}O_3$ (M + H) 279.1960, obsd 279.1967. For cyclopentanone **8**: (1.45 g, 27% as an oil, $[\alpha]^{20}_D$ −47.0 (*c* = 1.0, $CH_2Cl_2$); TLC $R_f$ = 0.25 (9:1 hexanes/EtOAc); $^1$H NMR $\delta$ 4.65 (dt, *J* = 4.9, 11.5 Hz, 1H), 2.49 (m, 1H), 2.16 (m, 3H), 1.93 (m, 3H), 1.75 (m, 1H), 1.60 (d, *J* = 12.1 Hz, 2H), 1.34−1.48 (m, 3H), 0.88−1.05 (m, 9H), 0.67 (d, *J* = 7.6 Hz, 3H); $^{13}$C NMR $\delta$ u 207.0, 167.6,

(15) For rhodium (II) complexes, see: (a) piv = pivalate: Handa, M.; Takata, A.; Nakao, T.; Kasuga, K.; Mikuriya, M.; Kotera, T. *Chem. Lett.* **1992**, *10*, 2085. (b) tfa = trifluoroacetate: Duddeck, H.; Ferguson, G.; Kaitner, B.; Kennedy, M.; McKervey, M. A.; Maguire, A. R *J. Chem. Soc., Perkin Trans. 1* **1990**, *4*, 1055. (c) oct = octanoate: Giroud-Godquin, A. M.; Marchon, J. C.; Guillon, D.; Skoullos, A. *J. Phys. Chem.* **1986**, *90*, 5502. (d) $Ph_3CO_2$ = triphenylacetate: Hashimoto, S.; Watanabe, N.; Ikegami, S *Tetrahedron Lett.* **1992**, *33*, 2709. (e) OAc = aceto Rempel, G. A.; Legzdins, P.; Smith, H.; Wilkinson, G. *Inorg. Synth.* **1971**, *13*, 90. (f) Esp = bis[rhodium (α,α,α′,α′-tetramethyl-1,3-benzenedipropionate)]: Espino, C. G.; Flori, K. W.; Kim, M.; Du Bois, J. D. *J. Am. Chem. Soc.* **2004**, *126*, 15378. (g) *R*-ptpa = dirhodium tetrakis[*N*-phthaloyl-(*R*)-phenylalaninate]: Okada, Y.; Minami, Y.; Miyamoto, M.; Otaguro, T.; Sawasaki, S.; Ichikawa, J. *Heteroatom Chem.* **1995**, *6*, 195. (h) *R*-pttl = dirhodium tetrakis[(2*R*)-3,3-dimethyl-2-(phthalimido)butanoate]: Tsutsui, H.; Yamaguchi, Y.; Kitagaki, S.; Nakamora, S.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2003**, *14*, 817. (i) *S*-dosp = dirhodium tetrakis[(*S*)-(−)-*N*-*p*-dodecylphenylsulfonyl)prolinate]: Davies, H. M. L.; Bruzinkski, P.; Hutcheson, D. K.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897. (j) *S*-tbsp = dirhodium tetrakis[1-[(4-*tert*-butylphenyl)sulfonyl]-(2*S*)-pyrrolidinecarboxylate], see ref 14i.

(16) $^{13}$C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" and for methylene and quaternary carbons as "u".

40.7, 37.7, 34.2, 33.6, 21.6, 20.7; d 74.9, 46.8, 32.2, 31.3, 26.2, 23.4, 22.0, 20.9, 16.3; IR 2950, 1735, 1454, 1384, 1311 $cm^{-1}$; MS *m/z* 279 (M + H, 100), 263 (49), 141 (98), 123 (79); HRMS calcd for $C_{17}H_{27}O_3$ (M + H) 279.1960, obsd 279.1967.

**Ketal 9.** 2,2-Dimethyl-1,3-propanediol (2.11 g, 24 mmol), *p*-toluenesulfonic acid monohydrate (5 mg, 0.02 mmol), and cyclopentanone **2** (3.33 g, 12 mmol) were combined in 24 mL of dry toluene. The solution was maintained at reflux for 8 h. The reaction was concentrated, and the residue was chromatographed to give the ketal **6** (3.89 g, 89% yield) as a white solid: mp = 97−99 °C; $[\alpha]^{20}_D$ +32.1 (*c* = 1.0, $CH_2Cl_2$); TLC $R_f$ = 0.49 (8:2 petroleum ether/MTBE); $^1$H NMR $\delta$ 4.69 (dt, *J* = 4.9, 11.5 Hz, 1H), 3.62 (d, *J* = 11.2 Hz, 1H), 3.47 (m, 3H), 2.43 (dd, *J* = 8.2, 13.6 Hz, 1H) 1.87−2.10(m, 4H), 1.66−1.74 (m, 3H), 1.39−1.48 (m, 5H), 1.14 (m, 2H), 1.06 (m, 3H), 0.868−1.05 (m, 7H), 0.74 (m, 6H); $^{13}$C NMR $\delta$ u 170.6, 107.1, 73.2, 71.7, 40.7, 37.0, 34.5, 30.2, 25.2, 23.6, 23.3, 23.0, 16.8; d 74.3, 47.0, 31.4, 26.0, 24.6, 22.1, 22.0, 20.8, 16.4; IR 2950, 1705, 1455, 1384, 1309 $cm^{-1}$; MS *m/z* 365 (M + H, 87), 279 (7), 227 (100), 209 (63), 182 (36), 141 (65), 128 (60); HRMS calcd for $C_{22}H_{36}O_4$ 364.2614, obsd 364.2623.

**(1*S*,5*R*)-5′,5′-Dimethyl-1*H*-spiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxane]-1-carbaldehyde 10.** $LiAlH_4$ (1.0 M solution in THF, 12 mL, 12 mmol) was added over 10 min to ketal **9** (3.64 g, 10 mmol) in 10 mL (1.0 M) of dry THF at rt. The solution was stirred at rt for 2 h. Ethyl acetate (5 mL) was added dropwise over 30 min followed by sodium sulfate decahydrate (3.2 g, 10 mmol). The mixture was stirred at rt for 2 h and then filtered through a pad of silica gel with ethyl acetate (20 mL) and concentrated. The residue was chromatographed to give the crude alcohol. Dess−Martin periodinane (4.24 g, 11 mmol) was added to the alcohol in 10 mL of dry dichloromethane at rt. The mixture was concentrated, and the residue was chromatographed to give the aldehyde **10** (1.62 g, 77% yield from **9**) as an oil: TLC $R_f$ = 0.34 (8:2 petroleum ether/MTBE); $[\alpha]^{20}_D$ −59.1 (*c* = 1.0, $CH_2Cl_2$); $^1$H NMR $\delta$ 10.36 (s, 1H), 3.72 (d, *J* = 11.2 Hz, 1H), 3.54 (d, *J* = 11.2 Hz, 1H), 3.48 (s, 2H), 2.47 (dd, *J* = 8.6, 14.3 Hz, 1H), 2.07 (m, 1H), 1.90 (m, 1H), 1.79 (m, 1H), 1.49 (dd, *J* = 5.2, 13.0 Hz, 1H), 1 30 (m, 3H), 1.17 (m, 2H), 0.77 (s, 3H); $^{13}$C NMR $\delta$ u 107.7, 73.3, 71.6, 44.8, 30.0, 25.6, 24.2, 18.6; d 201.1, 30.5, 22.9, 22.0; IR 2953, 1700, 1467, 1335, 1116 $cm^{-1}$; MS *m/z* 211 (M + H, 58), 181 (55), 141 (67), 123 (100); HRMS calcd for $C_{12}H_{18}O_3$ 210.1256, obsd 210.1262.

**(1*S*,5*R*)-1-[(1*Z*)-But-1-en-1-yl]-5′,5′-dimethylspiro[bicyclo[3.1.0]-hexane-2,2′-[1,3]dioxane] 3.** Potassium *tert*-butoxide (1.0 M solution in THF, 20 mL, 20 mmol) was added over 20 min to a suspension of propyltriphenylphosphonium bromide (3.50 g, 9 mmol) in 20 mL of dry THF at 0 °C. The external cooling was removed, and the mixture was stirred for 30 min. The aldehyde **10** (1.57 g, 7.5 mmol) was added, and the mixture was stirred at rt for 1 h. The mixture was quenched with water (50 mL) and then partitioned between water and EtOAc. The combined organic extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed to give the alkenyl cyclopropane **3** (1.84 g, 78% yield) as an oil: $[\alpha]^{20}_D$ +20.8 (*c* = 1.0, $CH_2Cl_2$); TLC $R_f$ = 0.74 (8:2 petroleum ether/MTBE); $^1$H NMR $\delta$ 5.70 (d, *J* = 8.0 Hz, 1H), 5.48 (m, 1H), 3.56 (d, *J* = 11.6 Hz, 1H), 3.43 (d, *J* = 11.6 Hz, 1H), 3.40 (s, 2H), 2.18−2.29 (m, 3H), 1.93 (m, 1H), 1.72 (dd, *J* = 8.0, 12.0 Hz, 1H), 1.41 (m, 1H), 1.17 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.85 (m, 1H), 0.71 (s, 3H), 0.65 (dd, *J* = 4.2, 7.2 Hz, 1H); $^{13}$C NMR $\delta$ u 110.0, 73.1, 71.4, 33.2, 30.1, 24.7, 24.6, 21.8, 14.7; d 136.6, 125.5, 22.7, 22.5, 22.1, 14.3; IR 2950, 2859, 1211, 1153, 1117 $cm^{-1}$; MS *m/z* 237 (M + H, 18), 201 (100), 183 (54), 141 (71); HRMS calcd for $C_{15}H_{24}O_2$ 236.1776, obsd 236.1767.

**(3a′*R*,7a′*R*)-6′-Ethyl-5,5-dimethyl-2′,3′,3a′,7a′-tetrahydrospiro[1,3-dioxane-2,1′-inden]-5′(4′*H*)-one 4.** To the alkenyl cyclopropane **3** (236 mg, 1.0 mmol) and potassium carbonate (280 mg, 2.0 mmol) in 10 mL of 2-propanol and 5 mL of tetrahydrofuran (0.075 M) was added $Fe(CO)_5$ (392 mg, 2.0 mmol). The Pyrex reaction vessel was purged with CO, a CO balloon was attached, and the mixture was irradiated for 4 h at room temperature as a thin film in a Rayonet apparatus (300 nm) set for autocooling. The reaction was halted every hour to agitate the tube inside the larger tube, after which photolysis was restarted. At the end of the irradiation, DBU (304 mg, 2.0 mmol) was added, and the mixture was stirred at room temperature for 1 h under nitrogen. The mixture was diluted with 40 mL of EtOAc and filtered through a small pad of packed silica gel. The eluate was concentrated and the residue was chromatographed to give 152 mg of unreacted **3** and 90 mg of **4** (98% yield based on **3** not recovered) as an oil: $[\alpha]^{20}_D$ +102.5 (*c* = 1.0, $CH_2Cl_2$); TLC $R_f$ = 0.30 (8:2 petroleum ether/MTBE); $^1$H NMR $\delta$ 6.45 (s, 1H), 3.45 (m, 4H), 2.95 (br s, 1H), 2.64 (m, 1H), 2.41 (m, 2H), 2.17 (m, 2H), 1.70- 1.97 (m, 3H), 1.35 (m, 1H), 0.95 (m, 6H), 0.85 (m, 3H); $^{13}$C NMR $\delta$ u 198.4, 140.7, 108.2, 71.4, 70.7, 39.9, 30.5, 29.3, 25.0, 21.7; d 138.9, 45.0, 33.1, 21.5, 21.3, 12.1; IR 2952, 1672, 1493, 1312, 1153 $cm^{-1}$; HRMS calcd for $C_{16}H_{24}O_3$ 264.1725, obsd 264.1731.

**(3a′*R*,6′*R*,7a′*S*)-6′-Ethyl-5,5-dimethylhexahydrospiro[1,3-dioxane-2,1′-inden]-5′(4′*H*)-one 14.** Pd/C (5 wt%, 10 mg) was added to the bicyclic enone **4** (85 mg, 0.32 mmol) in 5 mL of methanol. The reaction vessel was purged with hydrogen, a hydrogen balloon was attached, and the mixture was stirred at rt for 4 h until the TLC indicated disappearance of the UV absorbent spot. The mixture was filtered through a plug of Celite and concentrated. The residue was chromatographed to give **11** (81 mg, 95% yield) as an oil: $[\alpha]^{20}_D$ +124.6 (*c* = 1.0, $CH_2Cl_2$), TLC $R_f$ = 0.30 (8:2 petroleum ether/MTBE); $^1$H NMR $\delta$ 3.48 (m, 4H), 2.62 (m, 1H), 2.51 (m, 2H), 2.25 (dd, *J* = 5.6, 14.4 Hz, 1H), 2.15 (m, 1H), 2.00 (m, 3H), 1.82 (m, 2H), 1.46 (m, 1H), 1.24 (m, 2H), 1.04 (m, 3H), 0.91 (m, 6H); $^{13}$C NMR $\delta$ u 214.2, 109.6, 72.4, 71.5, 43.8, 30.7, 30.0, 28.3, 26.6, 22.3; d 49.2, 44.3, 37.1, 22.5, 11.6; HRMS calcd for $C_{16}H_{26}O_3$ 266.1882, obsd 266.1880.

**Methyl (3a′*S*,5′*S*,6′*R*,7a′*S*)-6′-Ethyl-5′-hydroxy-5,5-dimethyloctahydrospiro[1,3-dioxane-2,1′-indene]-4′-carboxylate 15.** Sodium hydride (60%, 24 mg, 0.6 mmol) and dimethyl carbonate (3 mL, 35 mmol) were heated to reflux for 20 min. A drop of methanol was added via an addition funnel over a condenser and stirred at reflux for 5 min. Bicyclic ketone **14** (80 mg, 0.3 mmol) in 1 mL dry toluene was added via an addition funnel over a condenser, and the mixture was stirred at reflux for 3 h. The mixture was cooled to rt and quenched with saturated aqueous $NH_4Cl$ and then partitioned between water and EtOAc. The combined organic extract was dried ($MgSO_4$) and concentrated. The residue was dissolved in methanol (5 mL), and $NaBH_4$ (19 mg, 0.5 mmol) was added. The mixture was stirred at rt for 2 h. The mixture was concentrated and the residue was chromatographed to give alcohol **15** (44 mg, 45% yield) as an oil: $[\alpha]^{20}_D$ +10.4 (*c* = 1.0, $CH_2Cl_2$); TLC $R_f$ = 0.19 (8:2 petroleum ether/MTBE); $^1$H NMR $\delta$ 4.17 (s, 1H), 3.72 (s, 3H), 3.50 (s, 2H), 3.42 (s, 2H), 2.64 (m 1H), 2.56 (m, 1H), 2.21 (m, 2H), 2.01 (m, 1H), 1.92 (m, 1H), 1.56 (m, 3H), 1.38 (m, 4H), 0.95 (m, 9H); $^{13}$C NMR $\delta$ u 176.1, 109.5, 72.7, 71.0, 31.6, 30.1, 30.0, 25.3, 22.3; d 67.6, 51.7, 46.8, 44.5, 42.0, 36.5, 22.5, 11.7; IR 3488, 2913, 1713, 1289, 1152 $cm^{-1}$; MS *m/z* 327 (M + H, 6), 141 (100); HRMS calcd for $C_{18}H_{30}O_5$ 326.2093, obsd 326.2095.

**Methyl (3a′*S*,6′*R*,7a′*S*)-6′-Ethyl-5,5-dimethyl-2′,3′,3a′,6′,7′,7a′-hexahydrospiro[1,3-dioxane-2,1′-indene]-4′-carboxylate 16.** Methanesulfonyl chloride (60 mg, 0.36 mmol) was added slowly to alcohol **12** (40 mg, 0.12 mmol) and triethylamine (1 mL, 7.2 mol) in 1 mL of dichloromethane at 0 °C. The solution was stirred to rt over 2 h. DBU (2 mL, 2.04 g, 14 mmol) was added, and the solution was stirred at rt for 18 h. The solution was filtered through a pad of silica gel with EtOAc and concentrated. The residue was chromatographed to give ketal ester **15** (21 mg, 56% yield) as an oil: $[\alpha]^{20}_D$ +25.5 (*c* = 1.0, $CH_2Cl_2$); TLC $R_f$ = 0.44 (8:2 petroleum ether/MTBE); $^1$H NMR $\delta$ 6.84 (s, 1H), 3.72 (s, 3H), 3.52 (s, 2H), 3.45 (d, *J* = 4.4 Hz, 2H), 2.95 (m 1H), 2.34 (m, 1H), 2.12 (m, 3H), 1.84 (m, 2H), 1.47 (m, 4H), 0.98 (m, 9H); $^{13}$C NMR $\delta$ u 185.1, 133.3, 109.5, 72.9, 71.2, 31.2, 30.1, 28.2, 27.7, 25.9; d: 143.2, 51.8, 42.8, 38.1, 36.0, 22.5, 11.3; IR 2958, 1714, 1440, 1249 $cm^{-1}$; MS *m/z* 309 (M + H, 8), 279 (7), 237 (12), 222 (94), 209 (37), 165

(55), 141 (100), 119 (99); HRMS calcd for $C_{18}H_{29}O_4$ (M + H) 309.2066, obsd. 309.2066.

**(+)-Coronafacic Acid 5.** Hydrochloric acid (20% aqueous, 2 mL) was added to ketal ester **16** (11 mg, 0.07 mmol). The mixture was heated to reflux for 4 h. The solution was allowed to cool to rt and then partitioned between water and EtOAc. The combined organic extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed to give **5** (7 mg, 55% yield) as an oil: TLC $R_f$ = 0.25 (7:3 petroleum ether/EtOAc); $[\alpha]^{20}_D$ +104 ($c$ = 0.1, MeOH) (lit.[14o] $[\alpha]^{20}_D$ +105). The spectroscopic data of the natural product **5** were compared with those of earlier syntheses[14o] and found to be identical.

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**Supporting Information Available:** General experimental procedures, details of the photochemical apparatus, preparation of **1**, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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