Synthetic Studies on Taxol. Assembly of the Bicyclo[5.3.1]undecane Moiety (AB Ring System) of Taxane Diterpenes

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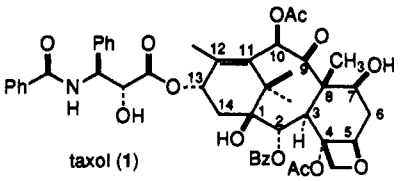
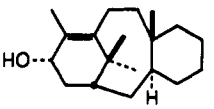
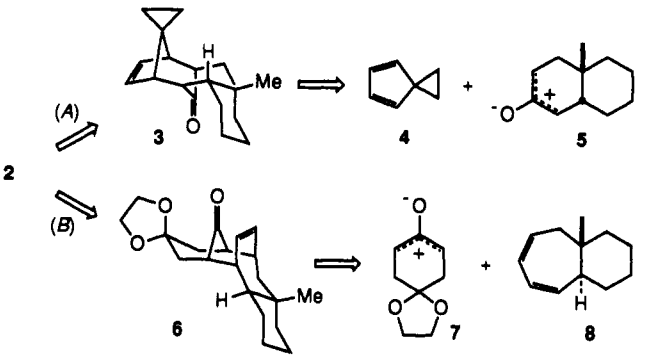
The architecturally complex, highly oxygenated taxane diterpenes, isolated from various yew (*Taxus*) species have continued to attract intense synthetic investigation.[2] In particular, taxol (1) has been the subject of extraordinary interest due to its promising antitumor activities.[3] It exhibits a unique mode of action on microtubule assembly.[4] Synthetic challenges are associated with not only an efficient construction of the tricyclic carbon skeleton, but the stereocontrolled introduction of the requisite functional groups.[5,6]



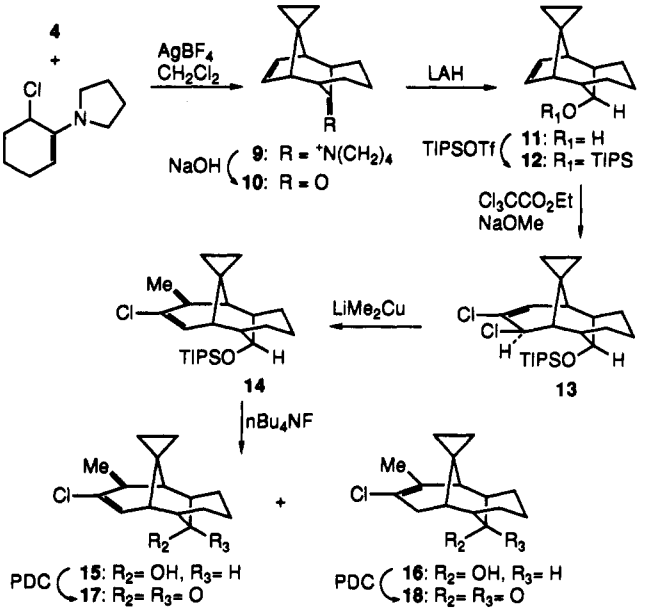


We envisioned that a quick entry into the taxane diterpenoid framework (2) would be available by employing a [4 + 3] diene–oxyallyl cycloaddition reaction.[7-9] As shown in Scheme I, a priori, there are two modes of such an approach which address the formation of the eight-membered central B ring through direct cycloaddition, followed by oxidative cleavage of the resulting either one- (route A) or two-carbon (route B) bridge.[10] The bridge present in the cycloadduct would be useful in not only providing suitable functionality for further elaboration, but also rigidifying the otherwise flexible conformation of the medium ring. Herein we report successful implementation of the strategy (A) to a AB ring construction of taxanes.

Scheme I



Scheme II



According to the elegant procedure of Schmid,[11] 3-chloro-2-pyrrolidinocyclohexene[12] underwent the desired [4 + 3] cycloaddition with spiro[2.4]hepta-4,6-diene (4)[13] in the presence of $AgBF_4$ to afford cycloadduct 9 (Scheme II). Subsequent basic hydrolysis provided ketone 10 in 42% overall yield. The stereochemical assignment was based on the known preference of oxylallyl cations to react in the endo mode.[7,11] On the other hand, no cycloadduct was obtained by employing the well-known oxyallyl cycloaddition methodology of Hoffmann or Noyori.[7]

The A-ring enlargement of adduct 10 by one C atom followed by unlatching the one-carbon bridge was required to generate the bicyclo[5.3.1]undecane moiety, the AB ring system of the taxanes. LAH reduction of ketone 10 gave exclusively the endo alcohol 11 (92% yield), which was then converted into TIPS-protected ether 12 (90% yield). Treatment of 12 with dichlorocarbene, generated from ethyl trichloroacetate and NaOMe, furnished allylic chloride 13 in quantitative yield (based on 80–95% conversion).[14] Chloride 13 was reacted with lithium di-

(1) Recipient of an NIH Research Career Development Award (GM-00575).

(2) For recent reviews on isolation and structure of taxanes, see: (a) Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425. (b) Gueritte-Voegelein, F.; Guénard, D.; Potier, P. *Ibid.* **1987**, *50*, 9. (c) Blechert, S.; Guenard, D. *The Alkaloids* **1990**, *39*, 195.

(3) (a) Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1991**, *56*, 6939 and references cited therein. (b) Borman, S. *Chem. Eng. News* **1991**, September 2, 11.

(4) Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665.

(5) For recent comprehensive reviews on synthetic approaches to taxanes, see: (a) Swindell, C. S. *Org. Prep. Proced. Int.* **1991**, *23*, 465. (b) Reference 2c. For recent developments, see also: (c) Wender, P. A. *Abstracts of Papers*; 203rd National Meeting of the American Chemical Society, San Francisco, CA; American Chemical Society: Washington, DC, 1992; ORGN 354. Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878.

(6) The first synthesis of a natural taxane, taxusin, was reported: Holton, R. A.; Juo, R. R.; Kim, H. B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558.

(7) For excellent reviews on the oxyallyl chemistry, see: (a) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163. (b) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (c) Mann, J. *Tetrahedron* **1986**, *42*, 4611.

(8) For related reactions of cyclopropanones and allene oxides, see: (a) Turro, N. J. *Acc. Chem. Res.* **1969**, *2*, 25. (b) Wasserman, H. H.; Berdahl, D. R.; Lu, T.-J. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; Vol. 2, Chapter 23. (c) Chan, T. H.; Ong, B. S. *Tetrahedron* **1980**, *36*, 2269.

(9) The term cycloaddition is used to indicate the overall bonding change rather than to imply a concerted mechanism.

(10) Our strategy for taxane skeleton construction differs from most of previous bond cleavage-based approaches in that a connection between C-2 and C-10 is broken in the formation of the 8-membered B ring (ref 5). For other examples of the C-2 and C-10 bond cleavage, see also: (a) Trost, B. M.; Hiemstra, H. *J. Am. Chem. Soc.* **1982**, *104*, 886. (b) Saha, G.; Bhattacharya, A.; Roy, S. S.; Ghosh, S. *Tetrahedron Lett.* **1990**, *31*, 1483.

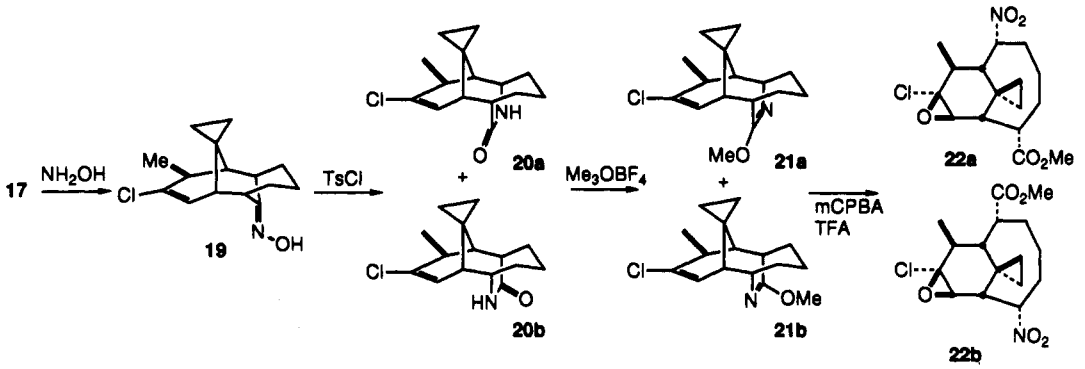
(11) Schmid, R.; Schmid, H. *Helv. Chim. Acta* **1974**, *57*, 1883.

(12) (a) Blazejewski, J. C.; Cantacuzene, D.; Wakselman, C. *Tetrahedron* **1973**, *29*, 4233. (b) Cf.: Comi, R.; Franck, R. W.; Reitano, M.; Weinreb, S. M. *Tetrahedron Lett.* **1973**, 3107.

(13) (a) Reimschneider, R.; Schönfelder, R. Z. *Naturforsch.* **1963**, *18b*, 979. (b) Commercially available from Aldrich Chemical Co.

0022-3263/92/1957-6664$03.00/0

Scheme III



methylcuprate to give 95% of the S_N2' product **14**, the stereochemical assignment of which rests on the difference NOE measurement. Desilylation (*n*-Bu_4NF, THF) of **14** afforded alcohol **15** (75–80%), along with a small amount (10–12%) of the regioisomeric olefin **16**. The latter olefin could be prepared in 65% yield (in addition to 20% of **15**) by prolonged treatment (48 h) and is presumably derived from the internally promoted isomerization due to the proximity of the endo hydroxyl group. Alcohols **15** and **16** were then converted (PDC, CH_2Cl_2) into ketones **17** and **18**, respectively, in 92% yield.

A Baeyer–Villiger oxidation of ketone **17** was originally envisaged to unravel the bicyclic framework to engender the AB ring skeleton of taxanes with suitable functionality for further elaboration. Not surprisingly, however, ketone **17** (as well as **10**) was recalcitrant toward Baeyer–Villiger oxidation.[15-17] Treatment of **17** with hydroxylamine gave a 3:2 mixture of two oximes **19**, which underwent a facile Beckmann rearrangement by the action of *p*-TsCl (in pyridine) to furnish the two regioisomeric lactams **20a,b** in a 3:2 mixture (72% overall).[18] Alkylation with Me_3OBF_4 then gave the corresponding imidates **21a,b** in quantitative yield (Scheme III). Finally, oxidation with mCPBA or mCPBA–TFA[19] produced, albeit in low (18%) yield, nitro esters **22a,b**, containing the AB ring skeleton of the taxanes with properly situated functionality.[20,21]

The structure and stereochemistry of **22a**, mp 113–115 °C, was unambiguously established by single-crystal X-ray analysis.

Further synthetic studies on the [4 + 3] cycloaddition with functionalized 3-chloro-2-pyrrolidinocyclohexenes, as well as a convergent azaallyl/oxyallyl cycloaddition approach to A + C → ABC ring construction of taxanes employing an optically active Wieland–Mischer ketone derivative, are currently in progress.

Experimental Section

***anti*-Spiro[cyclopropane-1,11′-tricyclo[4.3.1.1^{2,5}]undec-3′-en]-10′-one (10).** To a suspension of $AgBF_4$ (7.3 g, 37.4 mmol) in CH_2Cl_2 (150 mL) under nitrogen and in the dark was added at −78 °C spiro[2.4]hepta-4,6-diene (**4**) (6.4 mL, 63 mmol). To the resulting mixture was added dropwise (0.5 mL/min) at −78 °C crude 3-chloro-2-pyrrolidinocyclohexene (prepared from 30 mmol of 2-chlorocyclohexanone). The reaction mixture was allowed to warm to rt over 3–4 h. The precipitate was then removed by filtration through Celite. The filtrate was concentrated and diluted with water (150 mL). The aqueous layer was washed with benzene (2 × 50 mL). To the aqueous solution which contains immonium salt **9** were added NaOH (4.0 g) and MeOH (50 mL). The resulting mixture was then heated at reflux for 8 h. After a bulk of MeOH was removed under vacuum, the aqueous layer was extracted with ether (3 × 50 mL). The combined extracts were washed with 1 N HCl and brine, dried ($MgSO_4$), and concentrated to give crude **10** as a pale yellow solid. Purification by flash column chromatography on silica gel using 4:1 hexane–EtOAc as eluent gave 2.43 g (42%) of **10** as a white solid: mp 134–136 °C; IR ($CHCl_3$) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 0.28 (m, 2 H), 1.40 (m, 2 H), 1.54 (m, 1 H), 2.08 (m, 3 H), 2.15 (m, 2 H), 2.27 (m, 2 H), 2.45 (m, 2 H), 6.29 (m, 2 H); ^{13}C NMR (90 MHz) δ 8.9, 15.5, 18.4, 27.6, 31.1, 50.0, 51.9, 139.2, 219.5; HRMS (M^+) 188.1201 calcd for $C_{13}H_{16}O$, found 188.1204. Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.94; H, 8.58.

***anti*-Spiro[cyclopropane-1,11′-tricyclo[4.3.1.1^{2,5}]undec-3′-en]-*endo*-10′-ol (11).** To a solution of **10** (840 mg, 4.47 mmol) in anhydrous ether (40 mL) was added at 0 °C LAH (420 mg, 11.0 mmol). The reaction mixture was stirred for an additional 30 min at 0 °C and quenched with aqueous saturated $(NH_4)_2SO_4$ (0.8 mL). The resulting mixture was stirred at rt for 1 h. The precipitate was removed by filtration through Celite and washed thoroughly with ether. The combined filtrate was then dried ($MgSO_4$) and concentrated to give 800 mg (94%) of **11** as a white solid: mp 167–170 °C; IR ($CHCl_3$) 3600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.14 (m, 2 H), 1.16 (m, 2 H), 1.59 (m, 1 H), 1.71 (m, 2 H), 1.95 (m, 2 H), 2.00 (m, 3 H), 2.12 (m, 2 H), 2.72 (br s, 1 H), 3.64 (br s, 1 H), 6.57 (m, 2 H); ^{13}C NMR (90 MHz) δ 12.4, 15.6, 16.3, 27.5, 32.8, 39.3, 75.9, 141.6; HRMS (M^+) 190.1358 calcd for $C_{13}H_{18}O$, found 190.1361.

***endo*-10′-[(Triisopropylsilyl)oxy]-*anti*-spiro[cyclopropane-1,11′-tricyclo[4.3.1.1^{2,5}]undec-3′-ene] (12).** To a solution of **11** (800 mg, 4.21 mmol) in CH_2Cl_2 (15 mL) were added sequentially at 0 °C 2,6-lutidine (1.0 mL, 8.4 mmol) and TIPSOTf (1.4 mL, 5.2 mmol). The reaction mixture was stirred at rt for 2 h, quenched with water, and extracted with ether (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated.

(14) (a) Parham, W. E.; Schweizer, E. E. *J. Org. Chem.* **1959**, *24*, 1733. (b) Jefford, C. W. *Chimia* **1970**, *24*, 357. (c) Jefford, C. W.; Gunsher, J.; Hill, D. T.; Brun, P.; Le Gras, J.; Waegell, B. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 142. (d) Cf.: Seyferth, D.; Burlitch, J. M. *J. Am. Chem. Soc.* **1962**, *84*, 1757.

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(16) The lack of reactivity at the bridgehead carbonyl group might be due to its resistance to undergo rehybridization to sp^3 configuration. A similar behavior was noted by White for a structurally related bicyclic system [White, J. D. In *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press: Orlando, 1984; Chapter 13].

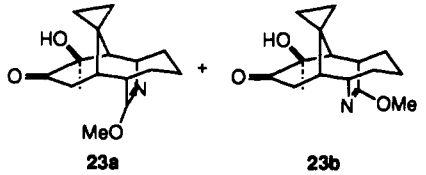
(17) A Baeyer–Villiger-type oxidation was accomplished by employing an α-alkoxy hydroperoxide through the Criegee rearrangement or the Kochi–Schreiber reaction sequence: Choi, J.-R.; Cha, J. K., unpublished results. Cf.: (a) Criegee, R.; Kaspar, R. *Liebigs Ann. Chem.* **1948**, *560*, 127. (b) Schreiber, S. L.; Liew, W.-F. *Tetrahedron Lett.* **1983**, *24*, 2363. (c) Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6163.

(18) Gawley, R. E. *Org. React.* **1988**, *35*, 1.

(19) Canan Koch, S. S.; Chamberlin, A. R. *Synth. Commun.* **1989**, *19*, 829.

(20) (a) Unoptimized yield. (b) The oxidative behavior of cyclic imidates toward other oxidizing agents is a subject of ongoing experimental efforts.

(21) Similarly, ketone **18** was also converted smoothly into the corresponding regioisomeric imidiates. Subsequent treatment with OsO_4 then gave hydroxy ketones **23a,b**.



The residue was purified by flash column chromatography on silica gel using hexane as eluent to give 1.31 g (90%) of **12** as a colorless oil: IR ($CHCl_3$) 1620, 1470, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.16 (m, 2 H), 0.97–1.20 (m, 23 H), 1.54 (m, 1 H), 1.70 (m, 2 H), 1.84 (m, 2 H), 1.91 (m, 2 H), 1.98 (m, 2 H), 2.10 (m, 1 H), 3.81 (br s, 1 H), 6.18 (m, 2 H); ^{13}C NMR (90 MHz) δ 12.0 (3 C), 12.6, 15.5, 16.5, 17.8, 18.1 (6 C), 27.4, 39.2, 50.6, 75.2, 138.0; HRMS (M^+) 346.2692 calcd for $C_{22}H_{38}OSi$, found 346.2666.

4′,*exo*-5′-Dichloro-*endo*-11′-[(triisopropylsilyl)oxy]-*anti*-spiro[cyclopropane-1,12′-tricyclo[5.3.1.1^{2,6}]dodec-3′-ene] (13). To a solution of **12** (2.63 g, 7.6 mmol) in hexane (300 mL) was added at 0 °C freshly prepared solid NaOMe (8.2 g, 0.152 mol). To the resulting mixture was added dropwise (over 8 h, 3 mL/h) at 0 °C ethyl trichloroacetate (25 g, 0.129 mol). The reaction mixture was allowed to warm to rt and stirred for an additional 8 h. The mixture was diluted with water and extracted with ether. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel, which was pretreated with 10% triethylamine in hexane, using hexane as eluent to give 3.0 g (93%) of **13** as a pale yellow oil: IR ($CHCl_3$) 1470, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.29 (m, 1 H), 0.76 (m, 2 H), 1.09 (m, 22 H), 1.28 (m, 1 H), 1.58 (m, 1 H), 1.74 (m, 2 H), 1.84–2.06 (m, 4 H), 2.18 (m, 2 H), 3.80 (br s, 1 H), 4.72 (s, 1 H), 6.19 (d, J = 6.5 Hz, 1 H); ^{13}C NMR (90 MHz) δ 12.0, 12.1 (3 C), 16.1, 17.1, 17.2, 18.1 (6 C), 30.6, 31.1, 38.3, 42.1, 45.2, 51.8, 66.5, 74.3, 133.2, 135.5; HRMS ($M^+ - C_3H_7$) 385.1521, 387.1491, and 389.1462 calcd for $C_{20}H_{31}Cl_2OSi$, found 385.1522, 387.1514, and 389.1498.

4′-Chloro-*exo*-5′-methyl-*endo*-11′-[(triisopropylsilyl)-oxy]-*anti*-spiro[cyclopropane-1,12′-tricyclo[5.3.1.1^{2,6}]dodec-3′-ene] (14). To a suspension of CuI (503 mg, 2.64 mmol) in anhydrous ether (10 mL) was added dropwise 3.5 mL of MeLi (1.5 M solution in ether, 5.25 mmol). The resulting mixture was stirred for an additional 20 min at 0 °C. A solution of **13** (570 mg, 1.3 mmol) in ether (5 mL) was then added at 0 °C. The reaction mixture was stirred for an additional 20 min at 0 °C, diluted with aqueous saturated NH_4Cl, and extracted with ether. The combined extracts were washed with concentrated NH_4OH, dried ($MgSO_4$), and concentrated. The crude product was purified by flash column chromatography on silica gel using hexane as eluent to give 506 mg (96%) of **14** as a colorless oil: IR ($CHCl_3$) 1620, 1470, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.25 (m, 1 H), 0.68 (m, 3 H), 1.07 (m, 21 H), 1.23 (m, 1 H), 1.26 (d, J = 7.3 Hz, 3 H), 1.43 (m, 2 H), 1.71 (m, 2 H), 1.88–2.20 (m, 5 H), 2.68 (dq, J = 0.7 and 7.3 Hz, 1 H), 3.83 (br s, 1 H), 5.92 (dd, J = 1.5 and 6.5 Hz, 1 H); ^{13}C NMR (90 MHz) δ 12.2 (3 C), 12.5, 16.1, 17.2, 18.1 (6 C), 18.2, 21.2, 31.0, 31.9, 39.0, 43.0, 44.8, 45.7, 49.9, 74.7, 129.7, 139.1; HRMS ($M^+ - C_3H_7$) 365.2067 and 367.2038 calcd for $C_{21}H_{34}ClOSi$, found 365.2054 and 367.2031.

4′-Chloro-*exo*-5′-methyl-*anti*-spiro[cyclopropane-1,12′-tricyclo[5.3.1.1^{2,6}]dodec-3′-en]-*endo*-11′-ol (15). To a solution of silyl ether **14** (550 mg, 1.35 mmol) in anhydrous THF (20 mL) were added sequentially at 0 °C powdered 4-Å molecular sieves (500 mg) and 2.2 mL of n-Bu_4NF (1.0 M solution in THF, 2.2 mmol). The resulting mixture was stirred for an additional 2 h at 0 °C. Sieves were removed by filtration and washed with ether (100 mL). The filtrate was washed with water, 1 N HCl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography on silica gel using 4:1 hexane–EtOAc as eluent to give 273 mg (80%) of **15** (R_f 0.40; mp 93–94 °C) and 34 mg (10%) of **16** (R_f 0.42; mp 69–72 °C): IR ($CHCl_3$) 3600, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.24 (m, 2 H), 0.72 (m, 2 H), 1.32 (d, J = 7.0 Hz, 3 H), 1.49 (m, 1 H), 1.57 (m, 2 H), 1.74 (m, 2 H), 1.97–2.20 (m, 5 H), 2.59 (br s, 1 H), 2.68 (dq, J = 1.6 and 7.0 Hz, 1 H), 3.78 (br s, 1 H), 6.18 (dd, J = 1.6 and 6.5 Hz, 1 H); ^{13}C NMR (90 MHz) δ 12.4, 16.0, 17.1, 18.0, 18.2, 21.0, 31.0, 31.8, 38.4, 42.4, 45.8, 49.6, 75.1, 132.1, 140.6; HRMS (M^+) 252.1281 and 254.1251 calcd for $C_{15}H_{21}ClO$, found 252.1266 and 254.1228.

4′-Chloro-3′-methyl-*anti*-spiro[cyclopropane-1,12′-tricyclo[5.3.1.1^{2,6}]dodec-3′-en]-*endo*-11′-ol (16). To a solution of silyl ether **14** (1.5 g, 3.68 mmol) in anhydrous THF (30 mL) were added sequentially at 0 °C powdered 4-Å molecular sieves (2.0 g) and 12.9 mL of n-Bu_4NF (1.0 M solution in THF, 12.9 mmol). The resulting mixture was stirred for 36 h at 60 °C. Sieves were removed by filtration and washed with ether (100 mL). The filtrate was washed with water, 1 N HCl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography on silica gel using 4:1 hexane–EtOAc as eluent to give 185 mg (20%) of **15** (R_f 0.40) and 603 mg (65%) of **16** (R_f 0.42): mp 69–72 °C; IR ($CHCl_3$) 3580 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.19 (m, 1 H), 0.38 (m, 1 H), 0.79 (m, 2 H), 1.36 (m, 2 H), 1.43 (m, 1 H), 1.72 (m, 2 H), 1.86 (t, J = 7.2 Hz, 3 H), 1.92–2.20 (m, 5 H), 2.45 (br s, 1 H), 2.77 (m, 2 H), 3.70 (br s, 1 H); ^{13}C NMR (90 MHz) δ 12.3, 17.9, 18.6, 19.8, 20.4, 31.5, 32.2, 37.2, 41.7, 41.9, 42.3, 50.7, 75.3, 128.7, 138.8.

4′-Chloro-*exo*-5′-methyl-*anti*-spiro[cyclopropane-1,12′-tricyclo[5.3.1.1^{2,6}]dodec-3′-en]-*endo*-11′-one (17). To a solution of **15** (220 mg, 0.88 mmol) in CH_2Cl_2 (20 mL) were added sequentially at 0 °C PDC (2.0 g, 5.3 mmol) and 4-Å molecular sieves (2.0 g). The reaction mixture was allowed to warm to rt over 2 h and diluted with ether (40 mL). The precipitate was removed by filtration through Celite, and the filtrate was then concentrated. The residue was purified by flash column chromatography on silica gel using 6:1 hexane–EtOAc as eluent to give 201 mg (92%) of **17** as a white solid: mp 77–78 °C; IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.43 (m, 1 H), 0.79 (m, 1 H), 0.99 (m, 2 H), 1.31 (d, J = 7.4 Hz, 3 H), 1.45 (m, 1 H), 1.55 (m, 1 H), 1.79 (m, 1 H), 2.18–2.28 (m, 6 H), 2.35 (m, 1 H), 2.43 (m, 1 H), 5.93 (m, 1 H); ^{13}C NMR (90 MHz) δ 9.5, 15.6, 16.8, 18.3, 20.6, 31.3, 33.1, 45.7, 48.9, 50.4, 53.0, 54.4, 129.5, 137.5, 219.4; HRMS (M^+) 250.1124 and 252.1095 calcd for $C_{15}H_{19}ClO$, found 250.1122 and 252.1101.

4′-Chloro-*exo*-5′-methyl-*anti*-spiro[cyclopropane-1,12′-tricyclo[5.3.1.1^{2,6}]dodec-3′-en]-*endo*-11′-one Oxime (19). To a solution of **17** (187 mg, 0.74 mmol) in a 1:1 mixture of MeOH–pyridine (20 ml) was added at once hydroxylamine hydrochloride (400 mg, 5.7 mmol). After being heated at 80 °C for 10 h, the reaction mixture was cooled to rt, treated with water (20 mL), and extracted twice with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 196 mg of oxime **19** as a pale yellow solid (~3:2 mixture of regioisomers). The crude product was used without further purification for next step. For an analytical sample, a 3:2 mixture of regioisomeric oximes was purified by column chromatography: mp 123–126 °C; IR ($CHCl_3$) 3610, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.28 (m, 2 H), 0.65 (m, 2 H), 0.86 (m, 4 H), 1.26 (d, J = 7.3 Hz, 3 H, **19b**), 1.28 (d, J = 7.3 Hz, 3 H, **19a**), 1.31 (m, 1 H, **19b**), 1.35 (m, 1 H, **19a**), 1.43 (m, 4 H), 1.60 (m, 1 H, **19a**), 1.68 (m, 1 H, **19b**), 2.01 (m, 8 H), 2.12 (m, 4 H), 2.42 (m, 2 H), 3.46 (br s, 1 H, **19a**), 3.55 (br s, 1 H, **19b**), 5.85 (d, J = 6.2 Hz, 1 H, **19b**), 5.93 (d, J = 6.2 Hz, 1 H, **19a**); ^{13}C NMR (90 MHz) δ (for **19a**) 9.9, 15.4, 17.4, 19.2, 20.4, 28.2, 31.0, 33.6, 44.0, 45.5, 48.2, 51.6, 128.4, 137.9, 163.4; (for **19b**) 10.2, 15.6, 17.6, 18.6, 20.6, 29.6, 30.0, 36.7, 40.9, 45.2, 47.9, 51.5, 128.9, 138.1, 164.0; HRMS (M^+) 265.1233 and 267.1204 calcd for $C_{15}H_{20}ClNO$, found 265.1229 and 267.1204.

Lactams 20a,b. To a solution of crude **19** (196 mg) in pyridine (20 mL) was added p-toluenesulfonyl chloride (500 mg, 2.6 mmol). The reaction mixture was stirred at rt for 8 h and heated at 80 °C for 4 h. After the solvent was removed under vacuum, the concentrate was filtered through silica gel to remove excess p-toluenesulfonyl chloride by using 9:1 CH_2Cl_2–MeOH as eluent. After evaporation of solvents, the residue was treated with water (15 mL) and CH_2Cl_2 (20 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated to afford 165 mg (87% overall from **17**) of pure **20a,b** as a white solid (~3:2 ratio of regioisomers): mp 155–165 °C; IR ($CHCl_3$) 3440, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.11 (m, 2 H), 0.45 (m, 2 H), 0.78–0.99 (m, 4 H), 1.09 (m, 1 H, **20b**), 1.15 (m, 1 H, **20a**), 1.32 (d, J = 7.2 Hz, 3 H, **20b**), 1.36 (d, J = 7.2 Hz, 3 H, **20a**), 1.47–2.02 (m, 14 H), 2.35 (q, J = 7.2 Hz, 1 H, **20a**), 2.49 (q, J = 7.2 Hz, 1 H, **20b**), 2.96 (m, 2 H), 3.50 (m, 2 H), 5.77 (d, J = 6.2 Hz, 1 H, **20b**), 5.97 (d, J = 6.2 Hz, 1 H, **20a**), 6.10 (br s, 1 H, **20b**), 6.41 (br s, 1 H, **20a**); ^{13}C NMR (90 MHz) δ (for **20a**) 8.2, 14.8, 17.0, 20.7, 21.0, 21.7, 26.4, 43.0, 43.5, 49.3, 50.7, 53.4, 126.8, 138.8, 177.3; (for **20b**) 8.3, 15.2, 17.4, 21.2, 21.6, 22.4, 24.9, 42.1, 47.1, 48.2, 50.8, 51.6, 126.9, 139.5, 177.2; HRMS (M^+) 265.1233 and 267.1204 calcd for $C_{15}H_{20}ClNO$, found 265.1222 and 267.1230.

Imidates 21a,b. To a solution of **20a,b** (150 mg, 0.5 mmol) in CH_2Cl_2 (20 mL) was added trimethyloxonium tetrafluoroborate (500 mg, 3.4 mmol). The reaction mixture was stirred overnight at rt, washed with aqueous K_2CO_3 solution, and dried ($MgSO_4$).

After the solvent was removed under vacuum, the crude product was purified by flash column chromatography on silica gel to give 131 mg (82%; 72% overall from **17**) of **21a,b** as a pale yellow oil (~3:2 ratio of regioisomers): IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.09 (m, 2 H), 0.39 (m, 2 H), 0.85 (m, 4 H), 1.00 (m, 1 H, **21b**), 1.11 (m, 1 H, **21a**), 1.28 (d, J = 7.3 Hz, 3 H, **21b**), 1.30 (d, J = 7.3 Hz, 3 H, **21a**), 1.40 (m, 4 H), 1.60–1.85 (m, 8 H), 1.95 (m, 4 H), 2.52 (m, 1 H, **21b**), 2.87 (m, 1 H, **21a**), 3.58 (s, 3 H, **21a**), 3.65 (s, 3 H, **21b**), 4.09 (m, 2 H), 5.80 (m, 1 H, **21b**), 5.86 (m, 1 H, **21a**); ^{13}C NMR (90 MHz) δ (for **21a**) 8.6, 14.9, 17.0, 20.7, 21.0, 22.3, 25.6, 42.6, 43.9, 46.3, 51.2, 52.9, 56.8, 126.9, 139.9, 167.0; (for **21b**) 8.5, 15.1, 18.0, 21.9, 22.1, 22.3, 23.9, 42.8, 47.0, 47.1, 48.7, 52.9, 55.4, 128.3, 136.8, 167.8; HRMS (M^+) 279.1390 and 281.1360 calcd for $C_{16}H_{22}ClNO$, found 279.1392 and 281.1357.

(1′*S,2′*R**,6′*S**,7′*S**,8′*R*,9′*R**,10′*S**)-6′-Carbomethoxy-9′-chloro-8′,9′-epoxy-10′-methyl-2′-nitrospiro[cyclopropane-1,11′-bicyclo[5.3.1]undecane] (22a) and Regioisomer 22b.** To a solution of **21a,b** (110 mg, 0.4 mmol) in CH_2Cl_2 (20 mL) were added sequentially at 0 °C 55% mCPBA (800 mg, 2.6 mmol) and trifluoroacetic acid (103 mg, 0.9 mmol). After being stirred at rt for 18 h, the reaction mixture was quenched with aqueous saturated Na_2CO_3 solution. The organic layer was washed with aqueous saturated K_2SO_3 solution and dried ($MgSO_4$). Removal of the solvent afforded 200 mg of the concentrate. Purification of the residue by column chromatography on silica gel using 4:1 hexane–EtOAc as eluent gave 25 mg (18%) of **22a,b** as a white solid (~3:2 ratio of regioisomers). For single-crystal X-ray analysis, a 3:2 mixture of **22a,b** was separated by preparative TLC, and the major product **22a** was then recrystallized from EtOAc: mp 113–115 °C; IR ($CHCl_3$) 1750, 1560, 1445, 1360, 1250, 1200, 1160, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.45 (m, 2 H), 0.62 (m, 1 H), 0.95 (m, 1 H), 1.15 (s, 1 H), 1.32 (d, J = 7.2 Hz, 3 H), 1.45 (m, 1 H), 1.69 (m, 1 H), 1.76 (s, 1 H), 1.97–2.20 (m, 2 H), 2.29–2.43 (m, 2 H), 2.50 (d, J = 10.8 Hz, 1 H), 2.80 (q, J = 7.2 Hz, 1 H), 3.68 (s, 3 H), 3.76 (s, 1 H), 4.41 (d, J = 9.8 Hz, 1 H); ^{13}C NMR (90 MHz) δ 6.6, 16.8, 18.9, 23.7, 28.8, 29.0, 29.3, 37.1, 42.4, 47.8, 51.0, 52.3, 64.4, 79.9, 93.6, 176.4.

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Registry No. **4**, 765-46-8; **9**, 144018-26-8; **10**, 144018-27-9; **11**, 144018-28-0; **12**, 144018-29-1; (±)-**13**, 144018-30-4; (±)-**14**, 144018-31-5; (±)-**15**, 144018-32-6; (±)-**16**, 144018-33-7; (±)-**17**, 144018-34-8; (±)-**18**, 144018-35-9; (±)-(*E*)-**19**, 144070-89-3; (±)-(*Z*)-**19**, 144018-36-0; (±)-**20a**, 144018-37-1; (±)-**20b**, 144018-38-2; (±)-**21a**, 144018-39-3; (±)-**21b**, 144018-40-6; (±)-**22a**, 144018-41-7; (±)-**22b**, 144018-42-8; (±)-3-chloro-2-pyrrolidinocyclohexene, 144018-25-7.

Supplementary Material Available: ^1H and ^{13}C NMR spectra of key intermediates (26 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

A Simple Three-Component Olefin Coupling Procedure

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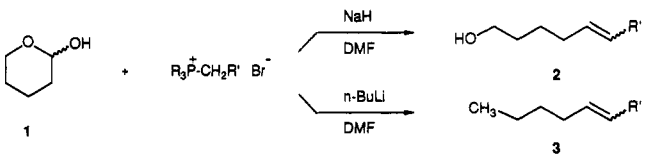
The Wittig olefination reaction remains among the most popular methods for preparing double-bond compounds from carbonyl or lactol precursors.[2] In many instances, the active phosphorus reagent can be generated in situ by deprotonation of the phosphonium salt with a strong base. During recent investigations in which unsaturated alcohols **2** were being prepared from δ-valerolactol (**1**), we observed the unusual formation of unsaturated adducts **3** in reactions for which *n*-butyllithium had been used as the base (Scheme I).

Scheme I



Scheme II

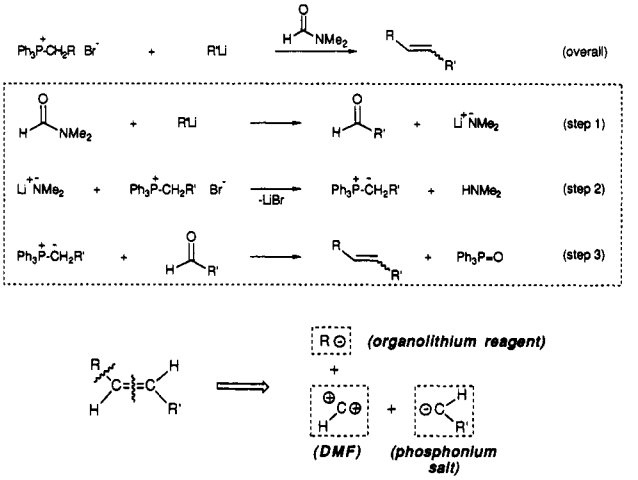


Figure 1.

Upon further examination, the butyl side chain of adducts **3** was found to be derived not from the starting lactol, but from *butyllithium*, with one of the new olefin centers of **3** arising from DMF. As illustrated in Figure 1, this olefination reaction can be viewed as a three-way coupling between a phosphonium salt, an organolithium reagent, and DMF. Mechanistically, the reaction presumably follows the stepwise pathway shown in Scheme II. Nucleophilic addition[3] of the organolithium reagent to DMF in step 1 generates an aldehyde[4] plus 1 equiv of dimethylamide anion. Subsequently, deprotonation of the phosphonium salt by dimethylamide anion gives the phosphorus ylide (step 2) which reacts with the aldehyde to give the olefin product (step 3). It is interesting to note that the organolithium reagent must undergo addition to DMF (step 1) more rapidly than it can deprotonate the phosphonium salt.

To study this one-pot olefin coupling procedure more fully, we surveyed several phosphorus reagents in reactions with *n*-butyllithium or phenyllithium in DMF. From the results listed in Table I, phosphonium salts which lead to stabilized ylides (entries 1–4) give the best yields. Entries 5 and 6 suggest that *phosphonate esters* can also be used in these reactions. On the other hand, reactions involving phosphonium salts of unstabilized ylides (entries 7–10) give

(1) Undergraduate research participant.

(2) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(3) Organolithium reagents typically undergo formylation reactions with DMF in the absence of strong proton donors. See: Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147. Traas, P. C.; Boelens, H. Takken, H. J. *Tetrahedron Lett.* **1976**, 2287.

(4) Variable amounts of the aldehyde are obtained in some of the reactions after aqueous workup. The aldehyde can be obtained cleanly if the reaction is carried out in the absence of the phosphonium salt and quenched with water.

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