Efficient Intramolecular C–H Insertion by an Alkylidene Carbene Generated from a Vinyl Chloride

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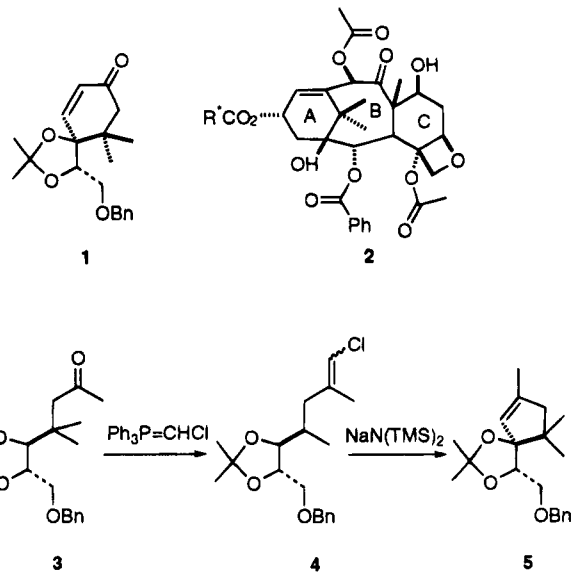
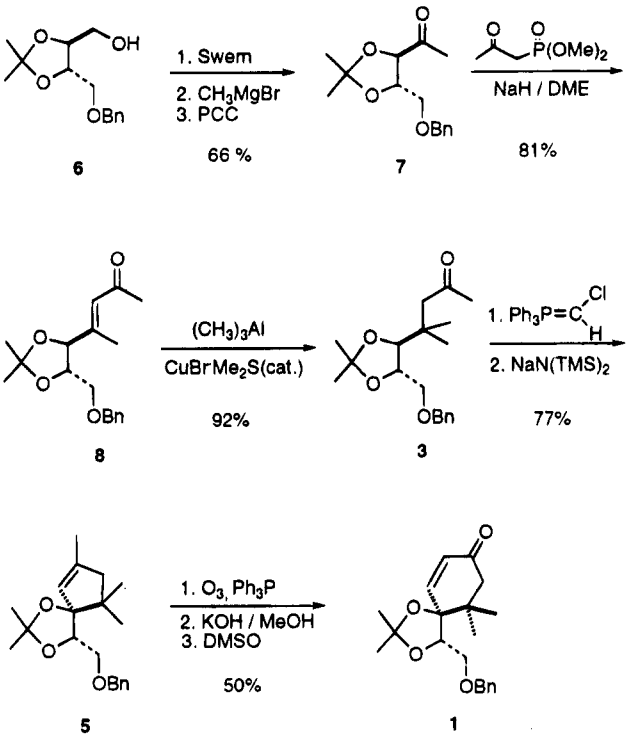
It is observed that chloride **4** on exposure to sodium bis(trimethylsilyl)amide smoothly generates the cyclopentene **5**, by insertion of the intermediate alkylidene carbene into the methine C–H. Chloride **4** is prepared in several steps from L-tartaric acid. On ozonolysis and subsequent aldol condensation, **5** is transformed into **1**, a synthon for the A ring of taxol **2**.

In support of our continuing studies toward the total synthesis of the antineoplastic diterpene taxol (**2**),[1–3] we required gram quantities of the enantiomerically pure enone **1**. We had previously reported a preparation of racemic **1**,[2] based on 1,5 C–H insertion of an alkylidene carbene that was generated by addition of the anion of (trimethylsilyl)diazomethane to racemic ketone **3**. We now report that the requisite alkylidene carbene can be generated much more economically by exposure of vinyl chloride **4** to excess sodium bis(trimethylsilyl)amide. We also describe a simple route to enantiomerically pure ketone **3**, and thus to enone **1**, from L-tartaric acid.



The starting point for the synthesis (Scheme 1) was the benzyl ether **6**, prepared, following published procedures,[4,5] from L-tartaric acid. Swern oxidation[6] followed

Scheme 1



by addition of methylmagnesium bromide and subsequent PCC oxidation[7] converted **6** into the methyl ketone **7**. It is intriguing that the simple ketone **7** has apparently not previously been reported.

Horner–Emmons condensation[8] of ketone **7** provided the enone **8**. We had anticipated that conjugate addition of lithium dimethyl cuprate to **8** might be difficult, as the γ-alkoxy substituent would be easily reduced. Indeed, lithium dimethyl cuprate addition proceeded in only about 40% yield. Fortunately, this situation was rescued by the recently-reported alternative[9] of CuBr-catalyzed Me_3Al conjugate addition. This variant provided a preparatively useful yield of the enantiomerically pure ketone **3**.

We were intrigued by the possibility that the simple vinyl chloride could be induced to cyclize.[10] We had previously reported the preparation of racemic **3**, and the generation and cyclization of the derived alkylidene carbene to give the racemic cyclopentene **5**, using as a reagent the lithium salt of (trimethylsilyl)diazomethane.[2] As we scaled up this reaction, the expense of the (trimethylsilyl)diazomethane led us to explore alternatives. While other routes to alkylidene carbenes have

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(1) Two elegant total syntheses of taxol have been reported: (a) Holton, R. A.; Kim, H.-B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeg, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599. (b) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulyannan, K.; Sorenson, E. J. *Nature*, **1994**, *367*, 630. (c) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A..; Sorenson, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624. (d) Nicolaou, K. C.; Liu, J. J.; Yang, Z.; Ueno, H.; Sorenson, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M..; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634. (e) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645. (f) Nicolaou, K. C.; Ueno, H.; Liu, J. J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Cadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653.

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been developed,[11,12] the vinyl chloride route offered advantages in simplicity and scalability.

In the event, condensation of ketone **3** with (chloromethylene)triphenyl phosphorane[13] proceeded smoothly, to give the vinyl chloride **4** as a mixture of geometric isomers. On exposure to an excess of sodium bis(trimethylsilyl)amide in toluene, this mixture was efficiently converted to the desired cyclopentene **5**. As expected,[10] we did not observe any competition from the alternative C–H insertion process, into one of the methyl groups.

Following our previously published procedure in the racemic series,[2] cyclopentene **5** on ozonolysis followed by aldol condensation and dehydration gave the enantiomerically-pure cyclohexenone **1**. Although racemic **1** is crystalline, the enantiomerically-pure enone **1** is an oil.

The observation reported here that alkylidene carbenes generated from vinyl chlorides can efficiently insert 1,5 into α-oxygenated C–H bonds, with retention of absolute configuration, substantially expands the utility and especially the scalabilty of this new approach[11c] to the preparation of enantiomerically-pure carbocycles from carbohydrates.

Experimental Section[15]

(4*R*,5*R*)-2,2-Dimethyl-5-[(phenylmethoxy)methyl]-1,3-dioxolane-4-methanol (6). To a flask containing L-tartaric acid (40.0 g, 0.23 mol) in 20 mL of reagent grade acetone was added 2,2-dimethoxypropane (71.8 g, 0.69 mol) and *p*-toluenesulfonic acid monohydrate (0.2 g, 1.05 mmol). The mixture was warmed with a heat gun to gentle reflux for 5 h. Removal of the solvent *in vacuo* followed by bulb-to-bulb distillation [pot = 90–100 °C (0.5 mm)] afforded the acetonide ester (49.7 g, 0.22 mol, 97% yield).

$LiAlH_4$ (8.0 g, 0.21 mol) in THF (200 mL) was chilled to 0 °C. The above ester (35.2 g, 0.16 mol) in 20 mL of THF was added dropwise. The mixture was warmed to rt overnight, and then was carefully quenched with 8 mL of water. The mixture was stirred for 20 min, 10% aqueous NaOH (8 mL) was added dropwise, the mixture was stirred for another 20 min, and then 24 mL of water was added. After filtration with EtOAc (3 × 20 mL), the combined filtrate was dried (K_2CO_3) and concentrated to give 23.3 g of the diol.

To a cold solution (0 °C) of diol (16.8 g, 0.10 mol) in 150 mL of DMF was added NaH (4.8 g, 0.12 mol, 60% in mineral oil). After the reaction subsided, benzyl bromide (18.8 g, 0.11 mol) was added. The reaction was stirred overnight and then was quenched with water (40 mL) and extracted with CH_2Cl_2 (2 × 40 mL). The combined organic extract was dried (K_2CO_3) and concentrated. The residue was chromatographed to give the known[5] alcohol **6** (14.0 g, 0.056 mol, 24% yield from L-tartaric acid) as a clear yellow oil: TLC R_f (20% EtOAc/petroleum ether) = 0.18; ^1H NMR δ 1.40 (s, 6H), 2.15–2.50 (bs, 1H), 3.40–4.20 (m, 6H), 4.57 (bs, 2H), 7.30 (bs, 5H).

(4*R*,5*R*)1-[2,2-Dimethyl-5-[(phenylmethoxy)methyl]-1,3-dioxolan-4-yl]ethanone (7). DMSO (2.82 mL, 40.0 mmol) was added slowly at −78 °C to a solution of oxalyl chloride (3.05 g, 24.0 mmol) in 100 mL of CH_2Cl_2. After the reaction subsided, alcohol **3** (5.0 g, 20.0 mmol) in 10 mL of CH_2Cl_2 was added dropwise over an additional 25 min. Triethylamine (8.0 mL, 80.0 mmol) was added dropwise, and then the reaction mixture was warmed slowly to rt. Water (20 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extract was dried (Na_2SO_4) and concentrated to give the crude aldehyde.[6]

To this *fresh* aldehyde in 100 mL of THF was added CH_3MgBr (20.0 mL, 60.0 mmol, 3.0 M solution in diethyl ether). After stirring for 4 h, the mixture was quenched with 1 N aqueous HCl to pH = 7.0. After extraction with 3 × 30 mL of EtOAc, the organic layer was dried (Na_2SO_4) and concentrated to give the crude alcohol (4.9 g).

The above alcohol (4.9 g) in 10 mL of CH_2Cl_2 was added to a flask containing PCC mixture (1:1:1 mixture by weight of PCC:4 A molecular sieve:NaOAc, ground together; 38.8 g, 60.0 mmol) in 100 mL of CH_2Cl_2. The resulting dark brown solution was stirred for 5 h and then was quenched with ether (30 mL). The mixture was filtered with ether (3 × 30 mL). The combined organic filtrate was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give 3.48 g (13.2 mmol, 66% yield from **6**) of ketone **7** as a clear pale yellow oil: TLC

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R_f (20% EtOAc/petroleum ether) = 0.57; $[\alpha]_D$ −12.6 ° (c = 0.18 g/100 mL in CH_3OH); ^1H NMR δ 1.44 (s, 3H), 1.48 (s, 3H), 2.27 (s, 3H), 3.60−3.77 (m, 2H), 4.19 (m, 1H), 4.21 (d, J = 2.1, 1H), 4.61 (s, 2H), 7.26−7.35 (m, 5H); ^{13}C NMR δ down: 26.1, 26.2, 26.7, 77.1, 81.8, 127.5, 128.1, 128.2; up: 70.1, 73.4, 110.8, 137.7, 207.9; IR (cm^{-1}) 2988, 2934, 2864, 2361, 1717, 1669, 1456, 1373; MS (*m/z*, %) 264 (24), 221 (46), 146 (86), 145 (54), 131 (100), 103 (86); HRMS calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1357.

(4*R*,5*R*)-2,2-Dimethyl-4-(1-methyl-3-oxo-1-butenyl)-5-[(phenylmethoxy)methyl]-1,3-dioxolane (8). To a flask containing dimethyl (2-oxopropyl)phosphonate[8] (346 mg, 2.08 mmol) and 3 mL of DME was added sodium hydride (50 mg, 1.25 mmol, 60% in mineral oil). After the white suspension was stirred for 5 min at 80 °C, a solution of ketone **7** (110 mg, 0.42 mmol) in 2 mL of DME was added dropwise, and the mixture was stirred at 80 °C for another 4 h. The mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford 16 mg of **4**, followed by 88 mg (81%) of enone **8** as a clear pale yellow oil: TLC R_f (20% EtOAc/petroleum ether) = 0.55; $[\alpha]_D$ −13.9° (c = 0.23 g/100 mL in CH_3OH); ^1H NMR δ 1.47 (s, 6H), 2.07 (s, 3H), 2.18 (s, 3H), 3.55−3.70 (m, 2H), 3.92−3.98 (m, 1H), 4.30 (d, J = 8.2 Hz, 1H), 4.56 (d, J = 12.1 Hz, 1H), 4.64 (d, J = 12.1 Hz, 1H), 6.29 (s, 1H), 7.26−7.45 (m, 5H); ^{13}C NMR δ down: 14.8, 26.8, 27.1, 31.8, 79.8, 82.1, 124.0, 127.8, 128.3, 129.3; up: 69.8, 73.6, 110.1, 138.0, 152.1, 197.4; IR (cm^{-1}) 2987, 2867, 1691, 1623, 1453, 1370, 1217; MS (*m/z*, %): 304 (5), 125 (100), 109 (55), 105 (59); HRMS calcd for $C_{18}H_{24}O_4$ 304.1675, found 304.1584. Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.92; H, 7.80.

(4*R*,5*R*)-2,2-Dimethyl-4-(1,1-dimethyl-3-oxobutyl)-5-[(phenylmethoxy)methyl]-1,3-dioxolane (3). To a stirred suspension of CuBr·Me_2S (13.6 mg, 0.066 mmol) in 2 mL of THF was added Me_3Al (0.73 mL, 1.45 mmol, 2.0 M solution in toluene) at 0 °C, followed by enone **8** (400 mg, 1.32 mmol) in THF (2 mL). The resulting black suspension was stirred at 0 °C for an additional 3 h and then was quenched with 10 mL of EtOH, followed by saturated aqueous NH_4Cl (10 mL). The mixture was filtered with THF (3 × 10 mL). After extraction with EtOAc (2 × 10 mL), the combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the ketone **3** (389 mg, 1.21 mmol, 92% yield) as a clear pale yellow oil: TLC R_f (20% EtOAc/petroleum ether) = 0.56; $[\alpha]_D$ −13.5° (c = 12.1 g/100 mL in CH_3OH); ^1H NMR δ 0.99 (s, 3H), 1.00 (s, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 2.09 (s, 3H), 2.33 (d, J = 15.4 Hz, 1H), 2.52 (d, J = 15.4 Hz, 1H), 3.52−3.55 (m, 2H), 3.81 (d, J = 7.7 Hz, 1H), 4.00−4.07 (m, 1H), 4.55 (d, J = 12.3 Hz, 1H), 4.61 (d, J = 12.3 Hz, 1H), 7.25−7.35 (m, 5H). This material was identical except in rotation with the racemic ketone previously prepared.[2]

(1*S*,5*R*)-3,3,7,9,9-Pentamethyl-5-[(phenylmethoxy)methyl]-2,4-dioxaspiro[4.4]non-6-ene (5). n-BuLi (2.3 mL of 2.34 M in hexane, 5.4 mmol) was added dropwise at 0 °C, with stirring, to diisopropylamine (0.58 g, 5.7 mmol) in THF (5 mL). After stirring for an additional 45 min, the mixture was cooled to −78 °C, and then (chloromethyl)triphenylphosphonium chloride[13] (2.05 g, 5.9 mmol) was added in portions. After stirring for 10 min at −78 °C, the colorless mixture was warmed to rt for 10 min. The mixture was cooled again to −78 °C, and then ketone **3** (0.87 g, 2.7 mmol) in 3 mL of THF was added dropwise over 5 min. The mixture was stirred and allowed to warm to rt over 18 h. Saturated aqueous NH_4Cl (10 mL) was added, followed by water (10 mL) and EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extract was dried (Na_2SO_4) and concentrated, and the residue was chromatographed to give the vinyl chloride **4** (0.82 g, 2.3 mmol, 86%) as a colorless oil: TLC R_f (20% EtOAc/petroleum ether) = 0.80; ^1H NMR δ 0.79 (s, 0.9H), 0.87 (s, 0.9H), 0.90 (s, 2.1H), 0.93 (s, 2.1H), 1.35 (s, 0.9H), 1.37 (s, 2.1H), 1.39 (s, 0.9H), 1.41 (s, 2.1H), 1.80 (s, 3H), 2.20 (s, 2H), 3.60 (m, 3H), 4.10 (m, 1H), 4.58 (s, 0.6H), 4.60 (s, 1.4H), 5.78 (bs, 0.3H), 5.92 (bs, 0.7H), 7.26−7.35 (m, 5H); IR (cm^{-1}) 2917, 1451, 1379, 1253, 1072.

Sodium bis(trimethylsilyl)amide (12.5 mL, 1.0 M in toluene, 12.5 mmol) was added dropwise, with stirring and cooling in an ice-bath, to neat vinyl chloride **4** (0.82 g, 2.3 mmol). The mixture was stirred for 18 h at rt. Saturated aqueous NH_4Cl (10 mL) was added, followed by water (10 mL) and EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extract was dried (Na_2SO_4) and concentrated, and the residue was chromatographed to give cyclopentene **5** (0.66 g, 2.1 mmol, 77% yield from **3**) as a colorless oil: TLC R_f (20% EtOAc/petroleum ether) = 0.80; $[\alpha]_D$ 7.3° (c = 1.40 g/100 mL in CH_3OH); ^1H NMR δ 0.94 (s, 3H), 1.10 (s,3H), 1.35 (s, 3H), 1.45 (s, 3H), 1.7 (d, J = 0.9 Hz, 3H), 1.84 (bd, J = 15.9 Hz, 1H), 2.25 (bd, J = 15.9 Hz, 1H), 3.46 (dd, J = 10.6, J = 2.3 Hz, 1H), 3.54 (dd, J = 10.5, J = 7.5 Hz, 1H), 4.20 (dd, J = 7.5, J = 2.3 Hz, 1H), 4.47 (d, J = 12.4 Hz, 1H), 4.70 (d, J = 12.4 Hz, 1H), 5.27 (m, 1H), 7.26−7.35 (m, 5H). This material was identical except in rotation with the racemic ketone previously prepared.[2]

(1*S*,5*R*)-5-[(Phenylmethoxy)methyl]-3,3,10,10-tetramethyl-2,4-dioxaspiro[4.5]dec-6-en-8-one (1). Into a −78 °C solution of the cyclopentene **5** (1.58 g, 5.0 mmol) in CH_2Cl_2 (30 mL) was bubbled a gentle stream of O_3/O_2 until the solution was faintly blue. Excess O_3 was subsequently purged with a stream of dry N_2, and then triphenylphosphine (1.60 g, 6.1 mmol) was added and the reaction was allowed to warm to 0 °C. After 1 h, the reaction was brought to rt and the solvent was removed *in vacuo*, and the residue was taken up in a solution of KOH (0.34 g, 6.1 mmol) in methanol (40 mL) at rt. After 2 h, the solution was neutralized to pH = 7 by the addition of 1 N aqueous HCl. The mixture was extracted with EtOAc (3 × 10 mL). The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was taken up in DMSO (25 mL), and the resulting solution was stirred at 150 °C for 3 h. After cooling, the mixture was diluted with water (50 mL) and extracted with EtOAc (4 × 30 mL). The combined organic extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed to give enone **1** (0.82 g, 2.5 mmol, 50% yield) as a colorless oil: TLC R_f (20% EtOAc/petroleum ether) = 0.65); $[\alpha]_D$ −9.8° (c = 1.04 g/100 mL in CH_3OH); ^1H NMR δ 1.01 (s, 3H), 1.14 (s, 3H), 1.43 (s, 3H), 1.49 (s, 3H), 2.30 (d, J = 16.3 Hz, 1H), 2.50 (d, J = 16.3 Hz, 1H), 3.51 (dd, J = 10.5, J = 3.65 Hz, 1H), 3.64 (dd, J = 10.5 J = 6.2 Hz, 1H), 4.41 (m, 5H), 4.47 (d, J = 12.1 Hz, 1H), 4.6 (d, J = 12.1 Hz, 1H), 5.96 (d, J = 10.3 Hz, 1H), 6.62 (d, J = 12.1 Hz, 1H), 7.26−7.35 (m, 5H). This material was identical except in rotation with the racemic ketone previously prepared.[2]

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Supporting Information Available: ^1H and ^{13}C spectra for compounds **7** and **8** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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