Synthesis and Palladium-Catalyzed Cycloaddition of the Bifunctional Conjunctive Reagent Methyl (*Z*)-1-Methyl-2-trimethylsilylmethyl-2-butenyl Carbonate

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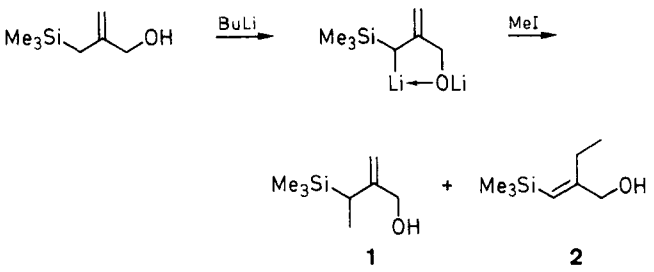
A simple synthesis of (*Z*)-2-trimethylsilylmethyl-2-buten-1-ol from 2-butyn-1-ol provides ready access to disubstituted bifunctional conjunctive reagents such as the title compound. Palladium(0) catalysts initiate cycloaddition to electron-deficient olefins to form methylenecyclopentanes with excellent regioselectivity.

The power of cycloadditions to increase molecular complexity rapidly is highlighted by the tremenduous importance that the Diels–Alder reaction has had in complex syntheses. Expansion of this capability would derive from the availability of cycloadditions to rings other than six members. 1,3-Dipolar cycloadditions creates five-membered heterocycles but is extremely limited in terms of carbocyclic synthesis.[1,2] Palladium-catalyzed cycloadditions have the promise of being rather general approaches to rings containing (2n + 1) members.[3,4] Utilizing 2-trimethylsilylmethallyl carboxylates, cycloadditions have created 5, 7 and 9 membered rings.[3] Introduction of substituents onto this four-carbon bifunctional conjunctive reagent complicates the cycloaddition tremendously in terms of both regio- and stereoisomers. Previous work established that good regioselectivity is observed with introduction of a single substituent.[5] In this paper, we explore the first example of the synthesis and cycloaddition of a dialkyl non-geminally disubstituted trimethylenemethane (TMM) precursor.

The magnitude of the problem just with respect to regioselectivity for a TMM precursor with two identical substituents is outlined in Scheme 1. If the substituents are non-identical, the number of regioisomers doubles. Combined with the fact that each regioisomer is a mixture of stereoisomers, practical considerations of analysis led us to limit our initial study to a case of identical substituents.

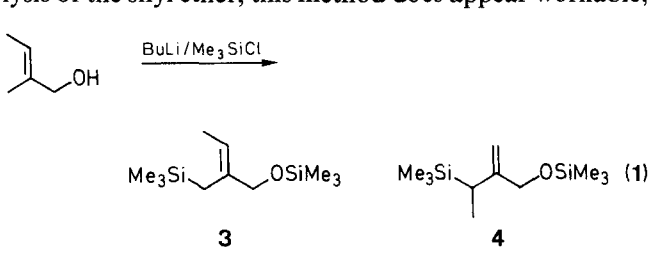
Synthesis of Bifunctional Conjunctive Reagents

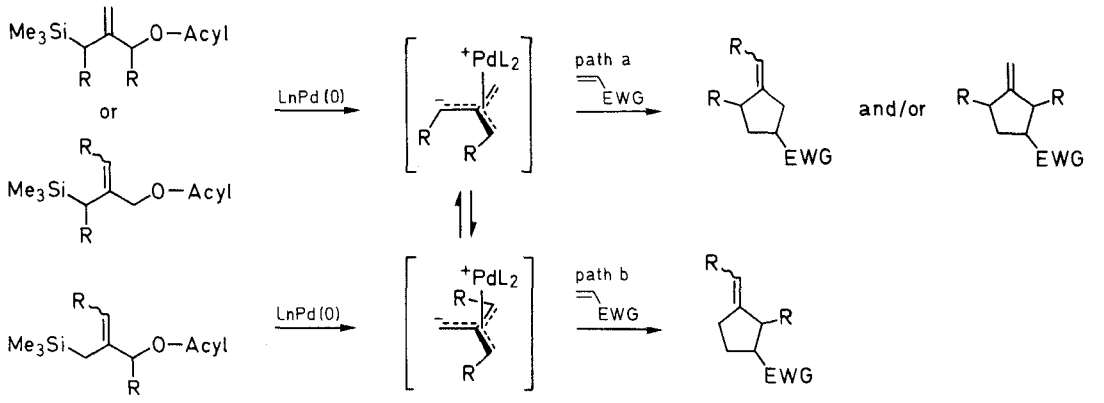
As depicted in Scheme 1, any of the three regioisomeric dimethylated bifunctional conjunctive reagents became our target (R = Me). Based upon our original method for the synthesis of the parent TMM precursor, we examined the metalation and alkylation of α-trimethylsilylmethallyl alcohol (Scheme 2).[6] Under our optimum conditions (10 M BuLi/in hexane, 1.1:1.5:1.0 THF/Et_2O/TMEDA, 0.5 M) whereby the metalation is performed at − 78 °C and the alkylation at − 78 °C to room temperature, a 41 % yield of a 3:1 ratio of alcohols **1** and **2** is obtained. These results indicate satisfactory metalation but modest regioselectivity in the alkylation. The moderate yield and the tediousness of the chromatographic separation induced us to seek a better alternative.



Scheme 2

Reversing the process, i.e. silylation of the dianion of 2-methyl-2-buten-1-ol, gives a 4:1 mixture of the desired products **3** and **4** (eq. 1). While decomposition occurred during our initial attempt to effect chemoselective hydrolysis of the silyl ether, this method does appear workable,

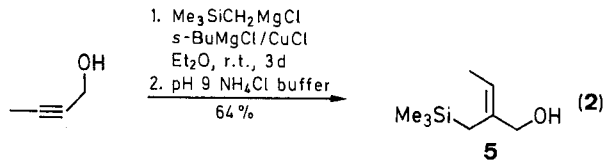




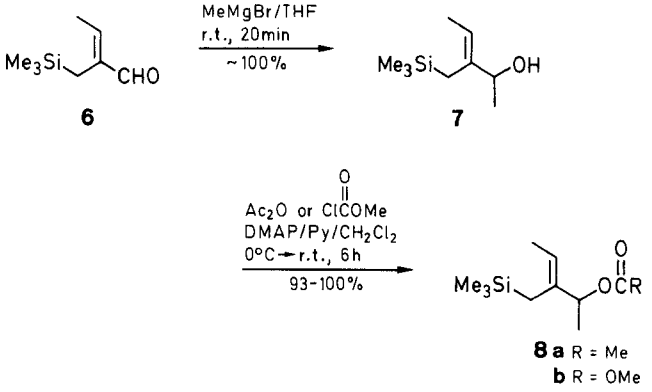
Scheme 1

nevertheless, the fact that a mixture of regioisomers still resulted induced us to seek a procedure free of this complication.

The carbacupration of propargyl alcohols holds promise to provide a single regioisomer (eq. 2).[7] The reaction is quite sensitive to the exact experimental parameters. Surprisingly, use of chloride as the sole halogen for *both* the organomagnesium and copper salts is necessary. In addition, the copper(I) chloride should be purified immediately prior to use.[8] Using these conditions with diethyl ether as solvent and purifying the product by distillation, a 64% yield of the desired alcohol is available on a multigram scale. The *Z*-geometry is assigned based upon literature precedent for the carbacupration–protonation.[7]



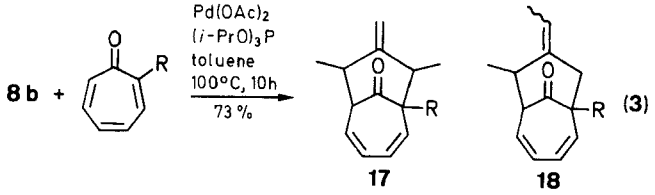
The corresponding aldehyde **6**, available by a Moffat–Swern oxidation[9] of the alcohol **5** (85% yield) readily allows for easy variation of the second substituent. For our purposes, we chose a methyl group as outlined in Scheme 3. This sequence should provide ready access to a diverse series of disubstituted bifunctional conjunctive reagents simply by choice of propargyl alcohol in eq. 2 and of Grignard reagent in Scheme 3.



Cycloadditions

Cycloaddition of carbonate **8b** with dimethyl benzylidenemalonate[10] using 5% palladium acetate, 30% triisopropyl phosphite, and 10% butyllithium in toluene at 70°C, conditions that proved optimum for the monomethylated TMM precursor, gives only an 18% yield of cycloadducts. Increasing the reductant, butyllithium,[5d] to 20% and the temperature to 80°C improves the yield to 42%. Best results (69% yield) are obtained at 100°C without butyllithium. The intractability of the regio- and stereoisomeric mixture induced us to effect an oxidative cleavage of the exocyclic double bond to the cyclopentanones. VPC analysis reveals a mixture of only four compounds in a ratio of 1.6:1.4:1.1:1.0. Base equilibration collapses this mixture of four to only two compounds which correspond to the two diastereomers of cyclopentanone **15**. The fact that the oxidative cleavage–equilibration proceeds in an overall 86% yield with no observable amounts of cyclopentanones **14** or **16** indicates a high regioselectivity for formation of adduct **9**.

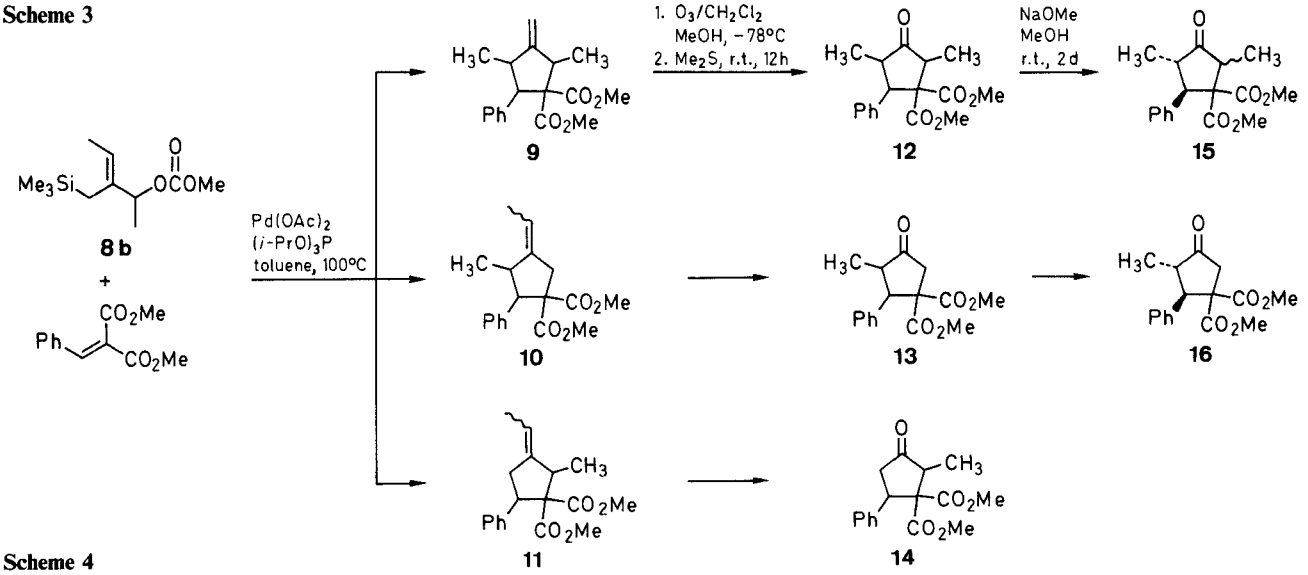
Cycloaddition of **8b** with tropone[11] gives the [6 + 3] cycloadducts[12] **17** (R = H) and **18** (R = H) in 73% yield. ^{1}H NMR analysis reveals both aliphatic (δ = 1.02–1.22) and vinylic (δ = 1.56–1.62) methyl groups. From the integrated intensities of these signals, we calculate the ratio of **17**/**18** at approximately 2:1. Utilizing 2-phenyltropone[13] as the acceptor decreases this ratio to about 1:1.



Discussion

For the synthesis of the disubstituted bifunctional conjunctive reagents that we employ as TMM synthons, carbacupration of the suitable propargylic alcohol provi-

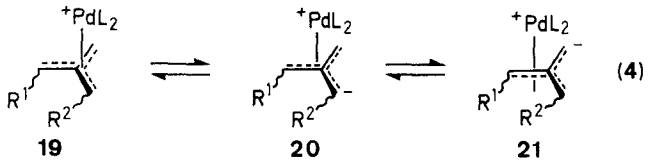
Scheme 3



Scheme 4

des the greatest flexibility and avoids the generation of isomers. As discussed previously, coordination of the metal with the oxygen presumably accounts for the regioselectivity. The requirements for chloride ion and ether as solvent support this notion. Chloride salts will be stronger Lewis acids and chloride is a better bridging ion if a bimetallic intermediate is involved. The lower Lewis basicity of ether diminishes the competition of solvent compared to substrate for coordination to the metal. Since one substituent derives from the choice of propargyl alcohol and the second substituent derives from choice of Grignard reagent, this strategy also allows for introduction of two different substituents at will.

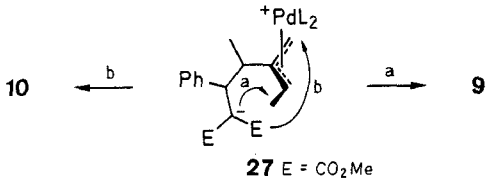
For cycloadditions, the specific regioisomeric starting material normally is irrelevant with respect to the regioisomeric nature of the products since interconversion of the presumed TMM-PdL_2 intermediates (eq. 4) is fast compared to the rate of cycloaddition for most acceptors.[5e,14] Furthermore, substituents on the anionic



(4)

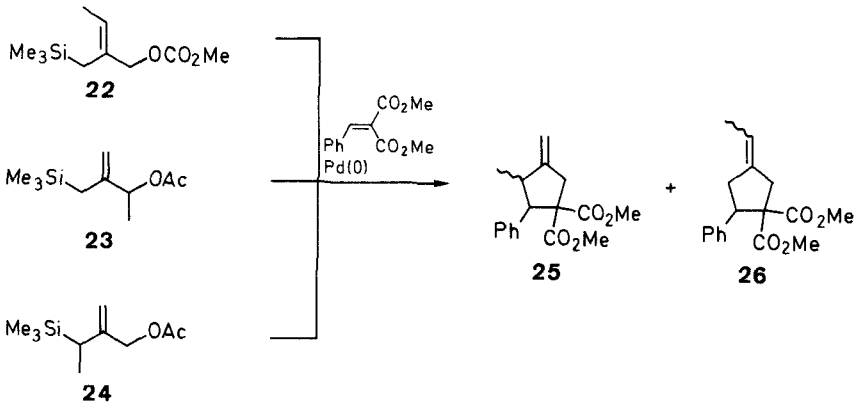
carbon of the TMM fragment stabilize that TMM-PdL_2 isomer regardless of the electronic nature of the substituent.[5c] The most stable TMM-PdL_2 appears to be responsible for the cycloaddition such that the carbon of the TMM fragment bearing the substituent becomes bonded to the terminal carbon of the acceptor. Relevant to the case here, all three monomethyl substituted TMM precursors **22**, **23** and **24** gave cycloadduct **25** as the dominant isomer.[5e] Conversion of alcohol **5** to carbonate **22** allows us to extend our study to the last regioisomer which also cycloadds with a regioselectivity comparable to that of **23**. The intermediate **19** (R^1 = Me, R^2 = H) as both the most stable and reactive isomer accounts for this selectivity.

For the dimethylated series, TMM-PdL_2 isomers **19** and **20** rather than **21** should account for the cycloadducts even though **21** should be the kinetic intermediate. The increased yield at higher temperatures presumably reflects the steric hindrance of the nucleophilic attack of **19** or **20** on the acceptor. The regioselectivity then derives from the second step as depicted in **27**.[15] Malonate nucleophiles have shown a propensity to attack the most electron deficient terminus in an unsymmetrical π-allylpalladium complex.[16] Thus, while the tendency to favor formation of **9** is thus expected, its exclusive formation is surprising.



The sensitivity of the regioselectivity of the second step to the exact nucleophile is evident by the switch to a [6 + 3] cycloaddition whereby a mixture derived from operation of both of the two possible paths is observed. In this case, increasing the steric hindrance of the nucleophile does indeed lead to enhanced preference for ring closure through path b although the effect is small. Ultimately, the regioselectivity will be determined by the specific acceptor. Most importantly, that regioselectivity can be high. Thus, highly substituted cyclopentanones are available through cycloaddition using disubstituted TMM-PdL_2 intermediates.

Reactions were generally conducted under a positive pressure of dry nitrogen within glassware which had been flame-dried under a stream of dry nitrogen. Reaction flasks were sealed with red rubber septa and were, unless otherwise mentioned, magnetically stirred. Anhydrous solvents and reaction mixtures were transferred by oven-dried syringe or cannula. Solvents and reagents were generally distilled immediately prior to use: MeCN, benzene, *t*-BuOH, 1,2-dichloroethane, CH_2Cl_2, diisopropylamine, DMSO, and pyridine from CaH_2; Et_2O and THF from sodium benzophenone ketyl; toluene and dioxane from molten sodium; acetone, MeOH, and DMF from $CaSO_4$, $Mg(OMe)_2$ and BaO respectively. $Pd(OAc)_2$ was recrystallized from benzene/AcOH. *O,N*-Bis(trimethylsilyl)acetamide (BSA) and triisopropyl phosphite were distilled from CaH_2. Flash chromatography following the method of Still[17] employed E. Merck silica gel (Kiesselgel 60, 230–400 mesh). Analytical TLC was performed with 0.2 mm coated commercial silica gel plates (E. Merck, DC-Plastikfolien, Kieselgel 60 F_{254}). ^1H NMR spectra were



Scheme 5

obtained and recorded from Gemini GEM-200 (200 MHz), Nicolet NT-300 (300 MHz) or Varian XL-400 (400 MHz) instrument, with TMS as internal standard. ^{13}C NMR spectra were recorded on a Nicolet NT-300 (75 MHz) or a Varian XL-400 (100 MHz) instrument. Chemical shifts are reported in δ units, parts per million from the central peak of $CDCl_3$ (δ = 77.0) as an internal reference. IR spectra were recorded on a Perkin-Elmer 1420 spectrophotometer in solution with 0.1 mm sodium chloride cavity cells. Mass spectral analyses were performed by the NIH Mass Spectral Facility at the school of Pharmacy, University of California - San Francisco on a Kratos MS-90 instrument with an ionizing current of 98 mA and an ionizing voltage of 70 eV. Microanalyses were performed by Robertson Laboratory, Inc. Madison, New Jersey.

(*Z*)-2-Trimethylsilylmethyl-2-buten-1-ol (5):
2-Butyn-1-ol (3.5 g, 3.8 mL, 50 mmol) was added slowly via syringe to a −20 °C solution of *s*-BuMgCl (2.0 M in Et_2O, 25 mL, 50 mmol) in Et_2O (120 mL). After 10 min at −20 °C, CuCl (500 mg, 5 mmol) was added all at once, quickly followed by addition of trimethylsilylmethylmagnesium chloride[18] (0.71 M in Et_2O, 70 mL, 50 mmol) via cannula. The reaction was allowed to reach r.t. where it was stirred for 3 d before being poured over a cold (0 °C) NH_4Cl pH 9 buffer solution (450 mL sat. NH_4Cl plus 50 mL sat. NH_4OH). The aqueous phase was separated and extracted with Et_2O (6 × 70 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude oil was purified by Kugelrohr distillation (bp 76 °C/~ 5 Torr) to give the title compound as a clear, colorless oil (5.03 g, 64 %).

IR ($CDCl_3$): ν 3600, 3380 (br), 2949, 2918, 2880, 1245 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.38 (q, J = 6.5 Hz, 1 H), 3.93 (d, J = 6.1 Hz, 2 H), 1.56–1.54 (m, 6 H), 0.00 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138, 117.6, 68.7, 18.3, 13.5, 1.0.

MS m/e (%): 158 (5.9), 157 (5.5), 149 (7.6), 148 (15.2), 147 (100), 144 (5.4), 143 (100), 141 (6.0), 130 (7.2), 129 (62.4), 127 (9.4), 115 (13.6), 103 (11.5), 91 (10.5).

HRMS: *m/z* Mass Calcd for $C_8H_{18}OSi$: 158.1127. Found: 158.1123.

(Z)-2-Trimethylsilylmethyl-2-butenal (6):
To a stirred solution of DMSO (728 mg, 660 µL, 4.9 mmol) in CH_2Cl_2 (16.2 mL) at −78 °C was added oxalyl chloride (619 mg, 425 µL, 4.9 mmol) dropwise via syringe. After stirring 15 min at −78 °C, a solution of alcohol **5** (670 mg, 4.24 mmol) in CH_2Cl_2 (5.0 mL) was added via cannula. After stirring 5 min at −78 °C, Et_3N (1.16 g, 1.6 mL, 11.4 mmol) was added. After stirring an additional 30 min at −78 °C, the cooling bath was removed and the reaction was allowed to reach r.t. After 45 min at r.t., the mixture was diluted with Et_2O (300 mL) and washed with water (50 mL), sat. $CuSO_4$ (2 × 50 mL) and then again with water (50 mL). The combined aqueous washings were back-extracted with Et_2O (50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography (hexane/Et_2O (20 1)) yields 530 mg (85 %) of the title compound, R_f = 0.52 (hexane/Et_2O (4: 1)). The sensitivity of the aldehyde led to its immediate use in subsequent additions.

IR ($CDCl_3$): ν = 2950, 1675, 1245 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.32 (s, 1 H), 6.42 (q, J = 7.1 Hz, 1 H), 1.89 (d, J = 7.1 Hz, 3 H), 1.72 (s, 2 H), −0.05 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.4, 146.3, 15.1, 14.1, −1.3.

(*Z*)-3-Trimethylsilylmethyl-4-penten-2-ol (7):
MeMgBr (1.25 mL of a 3.0 M solution in Et_2O, 3.7 mmol) was slowly added to a stirred r.t. solution of the aldehyde **6** (530 mg, 3.4 mmol) in THF (7.0 mL). After stirring 20 min at r.t., the reaction was cooled to 0 °C, diluted with Et_2O (100 mL) and quenched by the dropwise addition of sat. aq NH_4Cl (20 mL). The layers were separated and the organic phase was washed with brine (2 × 20 mL). The combined aqueous washings were back extracted with Et_2O (50 mL). The combined organic layers were then dried ($MgSO_4$), filtered and concentrated in vacuo. The crude oil was purified by Kugelrohr distillation (bp 158 °C/~ 5 Torr) to yield 583 mg (100 %) of the titled product as a clear, colorless oil, R_f = 0.15 (hexane/Et_2O (4:1)).

IR ($CDCl_3$): ν = 3600, 3430 (br), 2955, 2925, 2895, 1448, 1417, 1372, 1313, 1249, 1160, 1094, 1045, 972 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.41 (q, J = 6.6 Hz, 1 H), 4.07 (q, J = 6.5 Hz, 1 H), 1.64 (d, J = 13.8 Hz, 1 H), 1.53 (d, J = 6.6 Hz, 3 H), 1.41 (d, J = 13.8 Hz, 1 H), 1.34 (s, 1 H), 1.22 (d, J = 6.5 Hz, 3 H), 0.01 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.5, 115.0, 72.1, 22.1, 17.8, 13.5, −0.8.

MS: *m/z* (%) = 154 (11.2), 141 (5.8), 139 (9.4), 113 (4.1), 111 (10.1), 98 (11.5), 97 (11.8), 91 (20.4).

HRMS: *m/z* Calcd for $C_9H_{18}Si$ (M−H_2O): 154.1178. Found: 154.1162.

(Z)-4-Acetoxy-3-trimethylsilylmethyl-2-pentene (8a):
To a solution of alcohol **7** (263.5 mg, 1.53 mmol), DMAP (18.7 mg, 0.15 mmol), pyridine (604 mg, 618 µL, 4.6 mmol) and CH_2Cl_2 (765 µL) was cooled to 0 °C, Ac_2O (469 mg, 433 µL, 4.6 mmol) was added dropwise with stirring. Over 6 h the ice-bath was allowed to melt and the reaction to reach r.t. After evaporation in vacuo, the resulting viscous oil is purified by flash chromatography (hexane/Et_2O (20:1)) to yield 327 mg (100 %) of the titled compound as a clear, colorless oil, R_f = 0.72 (hexane/Et_2O (4:1)).

IR ($CDCl_3$): ν = 2965, 1725, 1324, 1253, 1042 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.42 (q, J = 7.3 Hz, 1 H), 5.19 (q, J = 6.5 Hz, 1 H), 2.01 (s, 3 H), 1.53 (d, J = 7.3 Hz, 3 H), 1.26 (d, J = 6.5 Hz, 3 H), 0.02 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 138.0, 117.9, 74.5, 21.1, 19.0, 17.9, 13.5, 0.8.

MS: *m/z* (%) = 214 (0.1), 155 (4.4), 139 (3.3), 133 (31.3), 117 (66.1), 91 (7.7), 82 (60.0), 81 (13.2), 75 (54.0), 73 (100.0), 67 (94.2).

HRMS: *m/z* Calcd for $C_{11}H_{22}O_2Si$: 214.1390. Found: 214.1390.

Methyl (*Z*)-1-Methyl-2-trimethylsilylmethyl-2-butenyl Carbonate (8b):
Methyl chloroformate (960 mg, 785 µL, 10.2 mmol) was slowly introduced via syringe into a 0 °C solution of alcohol **7** (583 mg, 3.4 mmol), DMAP (41.5 mg, 0.34 mmol) and pyridine (1.34 g, 1.4 mL, 17.0 mmol) in CH_2Cl_2 (6.3 mL). Over 6 h, the ice bath was allowed to melt and the reaction to reach r.t. After diluting with Et_2O (200 mL), the mixture was washed with water (950 mL), sat. $CuSO_4$ (2 × 20 mL) and then again with water (50 mL). The combined aqueous washings were back-extracted with Et_2O (50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography (hexane/Et_2O (9:1)) yields the title compound as a clear, colorless oil (731 mg, 93 %), R_f = 0.71 (hexane/Et_2O (4:1)).

IR ($CDCl_3$): ν = 2955, 1735, 1441, 1270, 1034 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 5.45 (q, J = 7.0 Hz, 1 H), 5.04 (q, J = 6.4 Hz, 1 H), 3.72 (s, 3 H), 1.57 (d, J = 14.0 Hz, 1 H), 1.53 (d, J = 7.0 Hz, 3 H), 1.46 (d, J = 14.0 Hz, 1 H), 1.32 (d, J = 6.4 Hz, 3 H), 0.10 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5, 137.4, 118.3, 78.7, 543, 19.2, 17.8, 13.6, −0.9.

MS: *m/z* (%) = 155 (7.6), 149 (24.3), 139 (2.7), 111 (4.7), 104 (5.9), 99 (5.3), 97 (5.2), 89 (100.0).

HRMS: *m/z* Calcd for $C_9H_{19}Si$ (M−OCO_2CH_3): 155.1257. Found: 155.1260.

Anal. Calcd for $C_{11}H_{22}O_3Si$: C,57.35; H, 9.62. Found: C, 57.29; H, 9.57.

General Procedure for Palladium-Catalyzed TMM Cycloadditions: A catalyst solution was prepared by dissolving $Pd(OAc)_2$ in toluene, adding triisopropyl phosphite at r.t. and then stirring at 60 °C for 15 min. Note: *This solution is prepared in excess so that an aliquot would deliver the total solvent and catalyst to a reaction (0.8 M, 5% Pd, 35% ligand based on the TMM precursor).* An aliquot of the above-

prepared catalyst solution was added via syringe to a mixture of the TMM precursor and the acceptor in a screw-cap reaction vial. Under an atmosphere of nitrogen, the septum was replaced with a Teflon-lined vial cap. The reaction was then stirred at 100 °C until complete consumption of the TMM precursor was indicated by TLC.

An aliquot of a freshly prepared catalyst solution [265 µL, containing: toluene (250 µL), $Pd(OAc)_2$ (2.24 mg, 0.01 mmol), triisopropyl phosphite (14.6 mg, 17.2 µL, 0.07 mmol)] was added to a screw-cap reaction vial containing TMM precursor **8b** (46.0 mg, 0.2 mmole) and dimethyl benzylidenemalonate[12] (88.0 mg, 0.4 mmol). The vial was sealed under an atmosphere of dry nitrogen and then heated 6 h at 100 °C. The crude reaction mixture was purified by flash chromatography (hexane/Et_2O (9:1)) to yield 41.8 mg (69 %) of a mixture of cycloadducts, R_f = 0.44 (hexane/Et_2O (4:1)).

Ozone was bubbled through a −78 °C solution of the above prepared cycloadducts (14.0 mg, 0.046 mmol) in CH_2Cl_2/MeOH (140 µL, 1 µL). When a faint color persisted, Me_2S (28.8 mg, 34 µL, 0.46 mmole) was added via syringe and the reaction was allowed to warm to r.t. After stirring 12 h at r.t. the crude reaction mixture was concentrated in vacuo. The resulting crude oil was purified by flash chromatography (hexane/Et_2O) (4:1)) to yield 12.4 mg (88 %) of the desired ketones as a 1.6:1.4:1.1:1 (VPC) mixture of diastereomers. GC: 50–250 °C at 10°C/min; t_R = 1635, 16.44, 16.28, 16.03 min, respectively.

NaOMe (86 µL of a 0.14 M solution in MeOH, 0.012 mmol) was added via syringe to the above prepared mixture of diastereomeric ketones. The reaction was stirred for 2 days at r.t. under nitrogen at which time it was filtered through a short column of silica gel and concentrated in vacuo to yield 12.1 mg (98 %) of the titled compounds as a 1.3:1 mixture of diastereomers (by ^1H NMR).

Flash chromatography of the crude reaction mixture yielded the pure cycloadducts. (2*R**,4*R*,*5*S**)- and (2*S**,4*R**,5*S**)-3,3-bis-(methoxycarbonyl)-2,5-dimethyl-4-phenylcyclopentanone **(15)**.

IR ($CDCl_3$): ν = 3040, 2960, 1750, 1730, 1458, 1440, 1280, 1260, 1220, 1155, 1150, 1080, 1060 cm^{-1}.

^1H NMR (300 MHz,$CDCl_3$): δ 7.35–7.20 (m, 10 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 3.57 (d, J = 12.4 Hz, 1 H), 3.45 (s, 3 H), 3.36 (s, 3 H), 3.25 (dd, J = 19.3, 1.6 Hz, 1 H), 2.98–2.84 (m, 2 H), 2.59 (q, J = 6.9 Hz, 1 H), 2.51 (d, J = 19.3 Hz, 1 H), 1.30 (d, J = 6.9 Hz, 3 H), 1.06 (t, J = 3.0 Hz, 3 H), 1.04 (t, J = 3.7 Hz, 3 H), 1.00 (d, J = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.9, 214.2, 171.3, 170.97, 169.2, 136.9, 136.8, 129.3, 128.9, 128.7, 128.6, 128.5, 128.46, 128.0, 127.9, 65.3, 59.7, 54.2, 52.7, 52.4, 52.3, 52.0, 51.9, 48.7, 46.4, 45.8, 45.7, 45.5, 14.1, 13.3, 12.7, 12.3, 9.9.

MS: *m/z* (%) = 304 (4.0), 290 (5.8), 245 (6.6), 244 (9.3), 230 (9.7), 216 (5.9), 202 (5.3), 159 (10.9), 154 (5.3), 145 (6.6), 143 (5.8), 140 (11.9), 129 (6.8), 128 (8.9), 127 (26.4), 126 (6.6), 119 (10.8), 119 (100.0), 117 (27.1), 115 (13.2), 107 (8.0), 91 (22.0).

HRMS: *m/z* Calcd for $C_{17}H_{20}O_5$: 304.1311. Found: 304.1304.

Anal. Calcd for $C_{17}H_{20}O_5$; C, 67.09; H, 6.62. Found: C, 67.14; H, 7.01.

7,9-Dimethyl-8-methylenebicyclo[4.3.1]decan-10-one (17, R = H) and 8-Ethylidene-7-methylbicyclo[4.3.1]decan-10-one (18, R = H):
Following the general procedure, an aliquot of a freshly prepared catalyst solution (265 µL containing: toluene (250 µL), $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) triisopropyl phosphite (14.6 mg, 17.2 µL, 0.07 mmole)) was added to a screw-cap reaction vial containing TMM precursor **8b** (46.0 mg, 0.2 mmol) and tropone[11] (42.4 mg, 0.4 mmol). The vial was sealed under an atmosphere of dry nitrogen and then heated for 10 h at 100 °C. The crude reaction mixture was directly purified by flash chromatography (hexane/Et_2O (10:1)) to yield 27.5 mg (73 %) of a 2:1 mixture of **17** (R = H) and **18** (R = H) respectively (each as a mixture of diastereomers; **17** (R = H) = 1.2:1.2:1; **18** (R = H) = 2:1, ratios by ^1H NMR, R_f = 0.65 (hexane/Et_2O (4:1).

IR ($CDCl_3$): ν 3042, 2982, 2940, 2890, 1709, 1609, 1692, 1460, 1384 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.94–5.66 (m, 2 H), 5.46–5.30 (m, 2.3 H), 4.90 (br s, 0.8 H), 4.81 (br s, 0.3 H), 3.38–3.19 (m, 1 H), 3.12–3.02 (m, 0.7 H), 2.95–2.46 (m, 2.2 H), 2.26 (dd, J = 13.5, 5.8 Hz, 0.2 H), 2.13 (d, J = 13.5 Hz, 0.2 H), 1.60 (d, J = 6.5 Hz, 0.4 H), 1.56 (d, J = 6.2 Hz, 0.8 H), 1.20 (d, J = 6.2 Hz, 0.8 H), 1.14 (d, J = 6.8 Hz, 1.0 H), 1.09 (d, J = 6.5 Hz, 1 H), 1.08 (d, J = 6.2 Hz, 1 H), 1.07 (d, J = 6.8 Hz, 0.8 H), 1.04 (d, J = 6.2 Hz, 0.4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.9, 209.5, 149.1, 148.9, 148.4, 134.4, 134.2, 129.0, 126.8, 126.7, 126.4, 126.2, 126.1, 124.7, 124.2, 124.1, 124.0, 123.9, 123.2, 123.1, 121.0, 112.5, 110.3, 109.9, 61.0, 60.9, 59.6, 59.4, 54.2, 54.1, 47.8, 43.2, 43.0, 42.4, 38.0, 36.3, 34.8, 28.8, 21.4, 20.6, 20.1, 14.5, 14.4, 14.3.

MS: *m/z* (%) = 189 (1.6), 18 (9.5), 173 (1), 159 (9.7), 145 (6.9), 108 (9.0), 107 (100), 105 (11.0), 94 (6.1), 92 (7.5), 91 (53.6), 85 (20.4).

HRMS: *m/z* for $C_{13}H_{16}O$: 188.1201. Found: 188.1197.

7,9-Dimethyl-8-methylene-1-phenylbicyclo[4.3.1]decan-10-one (17, R = Ph) and 8-Ethylidene-7-methyl-1-phenylbicyclo[4.3.1]decan-10-one (18, R = Ph):
Following the general procedure an aliquot of a freshly prepared catalyst solution (265 µL, containing: toluene (250 µL), $Pd(OAc)_2$ (2.24 mg, 0.01 mmol), triisopropyl phosphite (14.6 mg, 17.2 µl, 0.07 mmol)) was added to a screw-cap reaction vial containing TMM precursor **8b** (46.0 mg, 0.2 mmol) and 2-phenyltropone[13] (72.8 mg, 0.4 mmol). The vial was sealed under an atmosphere of dry nitrogen and then heated for 9 h at 100 °C. The crude reaction mixture was directly purified by flash chromatography (hexane/Et_2O (9:1)) to yield 15.8 mg (30 %) of a 1:1 mixture of **17** (R = Ph) and **18** (R = Ph) respectively (each as an intractable mixture of diastereomers, ratios by ^1H NMR, R_f = 0.49 (hexane/Et_2O (4:1)).

IR ($CDCl_3$): ν = 3075, 3040, 2980, 2940, 2890, 1709, 1695, 1658, 1504, 1461, 1455 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.06 (m, 3.7 H), 1.7–0.6 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.8, 207.6, 150.6–109.6 (54 signals), 63.9–12.1 (33 signals).

MS: *m/z* (%) = 265 (15.0), 264 (68.4), 249 (61.1), 236 (48.0), 235 (85.4), 183 (100), 165 (27.3), 152 (20.7), 129 (32.8), 128 (26.3), 115 (41.5), 111 (30.5), 107 (25.5), 105 (46.0), 103 (24.0), 91 (87.4).

HRMS: *m/z* Calcd for $C_{19}H_{20}O$: 264.1514. Found: 264.1511.

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