Transition Metal Catalyzed Stereospecific Intramolecular [3 + 2] Cycloadditions of Methylenecyclopropanes with Alkynes

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Abstract: Palladium catalyzed intramolecular [3 + 2] cycloadditions of diastereomerically pure methylenecyclopropanes MCPs have been investigated. The reaction was found to be stereospecific and occurred with retention of configuration at the carbon center undergoing reaction. A variety of substitution patterns were tolerated on and around the MCP. Deuterium labeling studies have been conducted, and information about the rate of the reaction was obtained. A mechanism has been proposed involving π-allyl intermediates. $Pd_2(dba)_3/P(OiPr)_3$ was a suitable catalyst for most cycloadditions, but molecular sieves or $Pd(PPh_3)_4$ improved the reaction with some substrates. 1,4-Addition of hydride or a carbanion to the enoate was achieved with high selectivity at the newly formed stereocenter. The allylic alcohol was selectively epoxidized with $VO(acac)_2$/*t*-BuOOH.

Introduction

An attractive strategy for the synthesis of five-membered rings is a transition metal mediated [3 + 2] cycloaddition reaction.[1] A variety of different three-carbon units has been employed in this process including trimethylenemethane (TMM)[2] synthons generated from bifunctional conjunctive reagents and methylenecyclopropanes MCPs.[3] In their seminal study, Noyori and Takaya reported that a Ni^0 complex catalyzed a [3 + 2] cycloaddition between MCP and an electron deficient alkene.[4] Many additional examples of this reaction have been reported, and improved catalysts were developed in the intervening years.[5] In particular Binger's comprehensive investigation of nickel and palladium catalyzed intermolecular cycloadditions between MCPs and alkenes or alkynes provided important insights into the reaction and revealed some limitations associated with a lack of regio- and stereoselectivity.[3a,d]

The regiochemical outcome of MCP cycloadditions was shown to depend on the substitution pattern of the substrate and the catalyst.[1,3] The trends that can be generalized from previous studies are as follows: (a) in the presence of Pd^0, all types of MCPs undergo distal ring opening regardless of the substitution pattern and (b) with Ni^0 catalysts the parent MCP undergoes proximal ring opening, whereas reaction of monosubstituted MCPs leads to distal and proximal ring opening and MCPs which bear dialkyl substituents at the cyclopropyl or vinylic carbon undergo distal ring opening preferentially. Exclusive distal ring opening occurs if the MCP is substituted with a diaryl moiety at the cyclopropane carbon or vinylic carbon.

Motherwell and Nakamura independently described the first examples of intramolecular cycloaddition using MCPs in the presence of palladium and nickel catalysts.[6] Intramolecular cycloaddition is entropically favored over intermolecular cycloaddition and occurs with complete regiochemical control.[7]

[⊗] Abstract published in *Advance ACS Abstracts,* September 1, 1996.

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(2) For reviews, see: (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. (b) Trost, B. M. *Pure & Appl. Chem.*, **1988**, *60*, 1615.

(3) For reviews, see: (a) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. (b) Ohta, T.; Takaya, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 1185. (c) Dzhemilev, U. M.; Khusnutdinov, R. I.; Tolstikov, G. A. *J. Organomet. Chem.* **1991**, *409*, 15. (d) Binger, P.; Fox, D. In *Methods Of Organic Chemistry* (Houben Weyl), Vol. E 21C, Part D, 1.6.1.2.3, p 2997.

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(5) (a) Binger, P. Schuchardt, U. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 249. (b) Binger, P. Schuchardt, U. *Chem. Ber.* **1980**, *113*, 3334. (c) Binger. P.; Lü, Q.-H.; Wedemann, P. *Angew. Chem., Int. Ed. Engl*. **1985**, *24*, 316.

(6) (a) Lewis, R. T.; Motherwell, W. B.; Shipman, M. *J. Chem. Soc., Chem. Commun.* **1988**, 948. (b) Bapuji, S. A.; Motherwell, W. B.; Shipman, M. *Tetrahedron Lett.* **1989**, *30*, 7107. (c) Motherwell, W. B.; Shipman, M. *Tetrahedron Lett.* **1991**, *32*, 1103. (d) Lewis, R. T.; Motherwell, W. B.; Shipman, M.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1995**, *51*, 3289. (e) Corlay, H.; Lewis, R. T.; Motherwell, W. B.; Shipman, M. *Tetrahedron* **1995**, *51*, 3303. (f) Yamago, S.; Nakamura, E. *J. Chem. Soc., Chem. Commun.* **1988**, 1112. (g) Yamago, S.; Nakamura, E. *Tetrahedron* **1989**, *45*, 3081. (h) Corlay, H.; Motherwell, W. B.; Pennell, A. M. K.; Shipman, M.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1996**, *52*, 4883.

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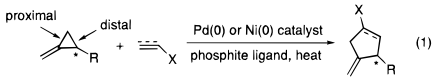
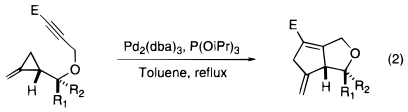
Despite significant effort on the synthetic, mechanistic, and theoretical aspects of the transition metal mediated MCP cycloaddition many details of the process are still uncertain. For example, prior to our work the stereochemical outcome of the stereocenter on the cyclopropane ring C* during the cycloaddition reaction was not known, eq 1.



In a preliminary report,[8] we showed that the palladium catalyzed intramolecular [3 + 2] cycloadditions of methylenecyclopropanes is stereospecific and occurs with overall retention of stereochemistry at the cyclopropane carbon, eq 2. We now describe in detail our studies on the scope and limitations of this methodology.

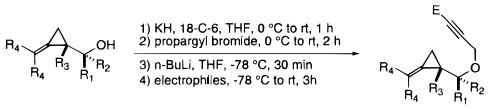


Cycloaddition Precursor Preparation

The viability of the cycloaddition study depended on ready access to diastereomerically pure MCPs.[9] The diastereoselective samarium promoted diiodomethane cyclopropanation of α-allenic alcohols provided easy access to a variety of diastereomerically pure substituted MCPs.[10] Starting from diastereomerically pure methylenecyclopropane carbinols, the precursors for the cycloaddition reaction were prepared in a straightforward manner, Table 1. Deprotonation of the alcohol with KH in the presence of 18-crown-6 followed by trapping the alkoxide with propargyl bromide leads to propargyl ethers in high yield. Lithiation of the terminal acetylene using *n*-butyllithium and trapping the resulting acetylide with different electrophiles provided a variety of precursors for the cycloaddition study.

Comparison of Ni^0 and Pd^0 Catalysts. We reported that Ni(COD)$_2$ catalyzed the intermolecular [3 + 2] cycloaddition between a diastereomerically pure methylenecyclopropane carbinol methyl ether and phenyl vinyl sulfone with synthetically useful levels of regio- and stereochemical control.[8] When the same partners were subjected to various Pd^0 catalysis, no reaction was observed. Similarly, attempts to react the MCP with dimethylactylenedicarboxylate as the C-2 unit or the bis TBDMS-ether of 1,4-butynediol led to polymerization of the alkyne. We had also attempted intramolecular [3 + 2] cycloadditions with Ni(COD)$_2$ as the catalyst using a variety of different substrates but in all cases observed the formation of complex mixtures whose structures were not easily identified. Therefore, Pd^0 was the catalyst used throughout our investigations.

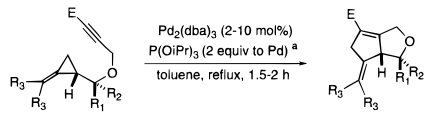
Table 1. Preparation of Precursors for [3 + 2] Cycloaddition



	Alcohols[a]	Propargyl Ethers (%)	Electrophile	Product (%)	E
1a	$R_1 = C_6H_{11}$, R_2 = H, R_3 = H, R_4 = H	**2a**(94)	$ClCOOCH_3$	**3a**(95)	$COOCH_3$
1a	$R_1 = C_6H_{11}$, R_2 = H, R_3 = H, R_4 = H	**2a**(94)	$(CH_2O)_n$	b **3b**(74)	CH_2OH
1a	$R_1 = C_6H_{11}$, R_2 = H, R_3 = H, R_4 = H	**2a**(94)		**3c**(99)	CH_2OTBS
1a	$R_1 = C_6H_{11}$, R_2 = H, R_3 = H, R_4 = H	**2a**(94)	CH_3CHO	**3d**(83)	CH_3CHOH
1a	$R_1 = C_6H_{11}$, R_2 = H, R_3 = H, R_4 = H	**2a**(94)		c **3e**(90)	CH_3CO
1a	$R_1 = C_6H_{11}$, R_2 = H, R_3 = H, R_4 = H	**2a**(94)	TMSCl	**3f**(99)	TMS
1a	$R_1 = C_6H_{11}$, R_2 = H, R_3 = H, R_4 = H	**2a**(94)	CH_3I[d]	**3g**(68)	CH_3
1b	R_1 = H, $R_2 = C_6H_{11}$, R_3 = H, R_4 = H	**2b**(82)	$ClCOOCH_3$	**4**(74)	$COOCH_3$
1c	$R_1 = C_7H_{15}$, R_2 = H, R_3 = H, R_4 = H	**2c**(85)	$ClCOOCH_3$	**5**(71)	$COOCH_3$
1d	R_1 = H, $R_2 = C_7H_{15}$, R_3 = H, R_4 = H	**2d**(87)	$ClCOOCH_3$	**6a**(78)	$COOCH_3$
1d	R_1 = H, $R_2 = C_7H_{15}$, R_3 = H, R_4 = H	**2d**(87)	TBDMSCl	**6b**(80)	TBDMS
1d	R_1 = H, $R_2 = C_7H_{15}$, R_3 = H, R_4 = H	**2d**(87)	$PhMe_2SiCl$	**6c**(96)	$SiPhMe_2$
1e	R_1, $R_2 = (CH_2)_5$, R_3 = H, R_4 = H	**2e**(41)	$ClCOOCH_3$	**7**(72)	$COOCH_3$
1f	$R_1 = C_6H_{11}$, R_2 = H, R_3 =H, R_4 = nPr	**2f**(57)	$ClCOOCH_3$	**8**(93)	$COOCH_3$
1g	$R_1 = C_6H_{11}$, R_2 = H, $R_3 = OCH_3$, R_4 = H	**2g**(84)	$ClCOOCH_3$	**9**(60)	$COOCH_3$
1h	$R_1 = C_6H_{11}$, R_2 = H, $R_3 = CH_3$, R_4 = H	**2h**(65)	$ClCOOCH_3$	**10**(85)	$COOCH_3$

[a] C_6H_{11} refers to cyclohexyl and C_7H_{15} refers to *n*-heptyl. [b] TBDMSCl, DMF, imidazole, room temperature. [c] PCC, NaOAc, CH_2Cl_2, room temperature. [d] HMPA was added as co-solvent.

Table 2. Stereospecificity of the Cycloaddition



Entry		Substrate[b]	Cycloadduct	Yield (%)
1	**3a**	$R_1 = C_6H_{11}$, R_2 = H, R_3 = H, E = $COOCH_3$	**11a**	75
2	**3b**	$R_1 = C_6H_{11}$, R_2 = H, R_3 = H, E = CH_2OH	**11b**	85 [c]
3	**4**	R_1 = H, $R_2 = C_6H_{11}$, R_3 = H, E = $COOCH_3$	**12**	72
4	**5**	$R_1 = C_7H_{15}$, R_2 = H, R_3 = H, E = $COOCH_3$	**13**	71
5	**6a**	R_1 = H, $R_2 = C_7H_{15}$, R_3 = H, E = $COOCH_3$	**14a**	70 (83)[d]
6	**7**	R_1 , $R_2 = (CH_2)_5$, R_3 = H, E = $COOCH_3$	**15**	68
7	**8**	$R_1 = C_6H_{11}$, R_2 = H, R_3 = nPr, E = $COOCH_3$	**16**	58

[a] P/Pd = 2/1; typically 2−10 mol % of $Pd_2(dba)_3$ was used. See experimental for details. [b] C_6H_{11} refers to cyclohexyl and C_7H_{15} refers to n-heptyl. [c] Reflux for 4 h. [d] 10 mol % of $Pd(PPh_3)_4$ was used at reflux in toluene for 2 h.

Stereospecificity. The Pd^0 catalyzed intramolecular [3 + 2] cycloaddition between a diastereomerically pure MCP tethered to an alkyne was shown to be a stereospecific reaction.[8] Thus, when **3a** was reacted with 2 mol % of $Pd_2(dba)_3$ and 8 mol % $P(OiPr)_3$, intramolecular cycloaddition took place in 75% yield and gave **11a** as a single diastereomer as determined by high field 400 MHz NMR (entry 1, Table 2). The diastereomeric starting material **4** afforded **12** in 72% yield using 5 mol % of $Pd_2(dba)_3$ and 20 mol % $P(OiPr)_3$ (entry 3, Table 2). The NMR spectra of diastereomers **11a** and **12** showed significant differences. For instance, the ^{1}H NMR (400 MHz) of **11a** has vinylic protons at 4.93 and 4.84 ppm, whereas in **12** the corresponding two signals are found at 5.10 and 4.93 ppm, respectively. This pattern is preserved for all the diastereomeric cycloadducts investigated, regardless of the substitution pattern. The reactions of **5** and **6a** proceeded in an identical fashion and were also stereospecific. Cycloaddition of the alcohol **3b** gave **11b** in

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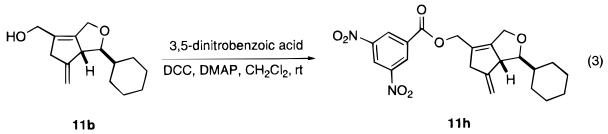
(9) For some examples of preparing methylenecyclopropanes, see: (a) Jonczyk A.; Kmiotek-Skarzynska I. *J. Org. Chem.* **1989**, *54*, 2756. (b) Jonczyk A.; Kmiotek-Skarzynska I.; Zdrojewski, T. *J. Chem. Soc., Perkin Trans. I* **1994**, 1605. (c) Ramaswamy, S.; Prasad, K.; Repic, O. *J. Org. Chem.* **1992**, *57*, 6344. (d) Staley, S. W.; Norden, T. D. *J. Am. Chem. Soc.* **1984**, *106*, 3699. (e) Stolle, A.; Ollivier, J.; Piras, P. P.; Salaün, J., de Meijere, A. *J. Am. Chem. Soc.* **1992**, *114*, 4051. (f) Heiner, T.; Michalski, S.; Gerke, K.; Kuchta, G.; Buback, M.; de Meijere, A. *Synlett* **1995**, 355. (g) Ollivier, J.; Piras, P. P.; Stolle, A.; Aufranc, P.; de Meijere, A.; Salaün, J. *Tetrahedron Lett.* **1992**, *33*, 3307. (h) Satoh, T.; Kawase, Y.; Yamakawa, K. *Tetrahedron Lett.* **1990**, *31*, 3609. (i) Satoh, T.; Kawase, Y.; Yamakawa, K. *Bull. Chem, Soc. Jpn.* **1991**, *64*, 1129. (j) Fischer, H.; Bidell, W.; Hofmann, J. *J. Chem. Soc., Chem. Commun.* **1990**, 858. (k) Padwa, A.; Wannamaker, M. W. *Tetrahedron* **1991**, *47*, 6139. (l) Petasis, N. A.; Bzowej, E. I. *Tetrahedron Lett.* **1993**, *34*, 943. (m) Achmatowicz, B.; Kabat, M. M.; Krajewski, J.; Wicha, J. *Tetrahedron* **1992**, *48*, 10201. (n) Baldwin, J. E; Adlington, R. M.; Bebbington, D.; Russel, A. T. *Tetrahedron* **1994**, *50*, 12015. (o) Köster, R.; Arora, S.; Binger, P. *Liebigs Ann. Chem.* **1973**, 1219. (p) Köster, R.; Arora, S.; Binger, P. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 205. (q) Köster, R.; Arora, S.; Binger, P. *Synthesis* **1971**, 322. For other methods, see references 6(d) and 6(e).

(10) (a) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1993**, *58*, 5037. (b) Lautens, M.; Delanghe, P. H. M. *J. Am. Chem. Soc.* **1994**, *116*, 8526. (c) Lautens, M.; Ren, Y. *J. Org. Chem.* **1996**, *61*, 2210.

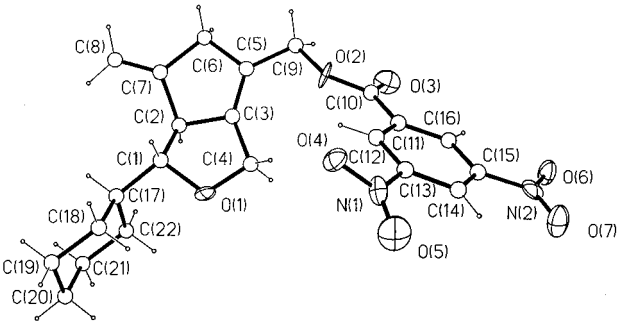
85% yield illustrating that the substituent on the acetylene does not influence the stereospecificity.

Determination of Relative Stereochemistry. Due to overlapping key resonances, NMR techniques (NOE, 2D NMR) failed to provide conclusive information on the relative stereochemistry of the cycloadducts. Instead, we obtained unequivocal proof by X-ray crystallography. Reduction of **11a** with DIBAL-H (−78 °C, THF) gave alcohol **11b** which was esterified (3,5-dinitrobenzoic acid, DCC, DMAP) to provide a crystalline product, **11h** (eq 3). Examination of the relative stereochemistry between the carbon bearing the cyclohexyl ring and that at the bridge revealed that the cycloaddition was not only stereospecific but also occurred with overall retention of stereochemistry.



11b **11h**

Substitution Effects. The two discoveries presented above suggested an investigation of the generality of the reaction be undertaken. Significant variation in reactivity has been observed as a function of the location and nature of the substituent as outlined below. Nevertheless, a wide variety of substitution patterns are tolerated leading to a diverse range of methylenecyclopentenes.

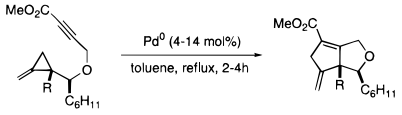


(a) Substitution on Carbinol Carbon. Substitution at R_1 and R_2 appears to have little effect on the stereoselectivity or reactivity of the reaction which was demonstrated by the successful cycloaddition of **7** (entry 6, Table 2).

(b) Substitution on the Exocyclic Methylene Group. A substrate with a dialkylidene moiety worked as well as one with a methylene group, and no scrambling of the carbon bearing the dialkyl substituents was observed (entry 7, Table 2). These observations mirror those of Motherwell who showed that no migration occurred in a Pd^0 catalyzed cycloaddition of a MCP with a diphenylmethylene group although migration is often observed in Pd^0 catalyzed intermolecular cycloaddition reactions.[3a,6d]

(c) Substitution on the Cyclopropane Carbon. Substitution at the sp^3 carbon on the methylenecyclopropane has a marked effect on the success of the cycloaddition (Table 3). While the reaction of **3a** (R = H, entry 1, Table 3) and **9** (R = OCH_3, entry 2, Table 3) were straightforward, treatment of **10** (R = Me, entry 3, Table 3) with either $Pd_2(dba)_3$ or $Ni(COD)_2$ gave a complex mixture of diene-containing products. Fortunately, we found that $Pd(PPh_3)_4$ catalyzed the [3 + 2] cycloaddition of **10** and gave the desired cycloadduct in 43% yield accompanied by some diene (entry 4, Table 3). It should be noted that Motherwell reacted a related compound and diene formation was also observed.[6e] However, a carbon analog gave the cycloadduct in 54% yield which implied that the oxygen on the tether played a role in influencing the reaction pathway.[6e]

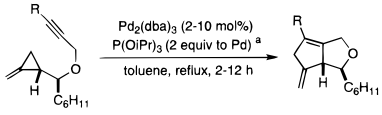
Table 3. Effect of Substituent on the Cyclopropane Carbon



Entry	Substrate [a]	R	Catalyst [b]	Cycloadduct	Yield (%)
1	**3a**	H	$Pd_2(dba)_3$ / $P(OiPr)_3$	**11a**	75
2	**9**	OCH_3	$Pd_2(dba)_3$ / $P(OiPr)_3$	**17**	75
3	**10**	CH_3	$Pd_2(dba)_3$ / $P(OiPr)_3$	**18**	complex mixture
4	**10**	CH_3	**$Pd(PPh_3)_4$**	**18**	**43**

[a] C_6H_{11} refers to cyclohexyl. [b] P/Pd = 2/1; typically 2−12 mol % of Pd^0 was used. See experimental for details.

Table 4. Effect of Substituent on the Acetylene



Entry	Substrate [b]	R	Catalyst	Cycloadduct	Yield (%)
1	**3a**	$COOCH_3$	$Pd_2(dba)_3$ / $P(OiPr)_3$	**11a**	75
2	**3b**	CH_2OH	$Pd_2(dba)_3$ / $P(OiPr)_3$	**11b**	85
3	**3c**	$CH_2OTBDMS$	$Pd_2(dba)_3$ / $P(OiPr)_3$	**11c**	100
4	**3e**	$COCH_3$	$Pd_2(dba)_3$ / $P(OiPr)_3$/ 4Å MS	**11e**	52 (92) [c]
5	**3g**	CH_3	$Pd_2(dba)_3$ / $P(OiPr)_3$	**11g**	< 5 [d]

[a] P/Pd = 2/1; typically 2−10 mol % of $Pd_2(dba)_3$ was used. See experimental for details. [b] C_6H_{11} refers to cyclohexyl. [c] 11 mol % of $Pd(PPh_3)_4$ was used at reflux in toluene for 1.5 h. [d] A similar result was observed when $Pd(PPh_3)_4$ was used as the catalyst.

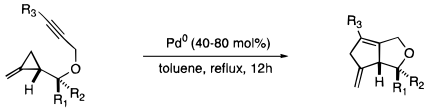
(d) Substitution on the Alkyne. The substituent on the acetylenic carbon had a significant influence on the success of the cycloaddition. Alkynes bearing an electron withdrawing group including an ester or ketone moiety underwent smooth cycloaddition to give the cycloadduct in good yield. Substrates bearing weaker electron withdrawing groups such as a hydroxymethyl or a protected hydroxymethyl group gave excellent yields of the cycloadduct. The successful cycloaddition of compound **3c** (entry 3, Table 4) indicates that the hydroxy oxygen does not play a role in delivering the palladium.[6c] Surprisingly, in a substrate with a methyl substituent, **3g** (entry 5, Table 4), only a very small amount of the desired cycloadduct was formed with large amounts of unreacted starting material. This result is in sharp contrast to the intermolecular cycloaddition of simple unsubstituted methylenecyclopropanes where nonactivated alkenes also undergo cycloaddition.[3a]

The cycloaddition of a substrate containing an alkyne bearing a silicon was studied since the product would contain a vinyl silane which upon protodesilylation would generate an adduct equivalent to a cycloaddition with a terminal alkyne, a reaction that failed to occur under these conditions. Alternatively, transformation of the vinylsilane to a ketone would lead to products that are equivalent to a formal reaction of a ketene with a MCP.

Ni^0/phosphite catalyzed intermolecular [3 + 2] cycloaddition between MCP and alkynylsilanes is a well established reaction.[5c] However, when Motherwell studied the intramolecular reaction, all attempts to cyclize a silyl substituted acetylene were unsuccessful.[6e]

We found the reaction was very sluggish with **3f** but did occur using 40−50 mol % $Pd_2(dba)_3$ or $Pd(PPh_3)_4$, (entry 1, Table 5). However, the TBDMS derivative **6b** (entry 2, Table 5) and $PhMe_2Si$ derivative **6c** (entry 4, Table 5) failed to yield any cycloadduct under $Pd_2(dba)_3$ catalysis. Only when 4 Å molec-

Table 5. Effect of Silicon Substituent on the Acetylene



Entry	Substrates [a]		R_3	Catalyst [b]	Cycloadduct	Yield (%)
1	**3f**	$R_1 = C_6H_{11}$, $R_2 = H$	TMS	$Pd(PPh_3)_4$	**11f**	46
2	**6b**	$R_1 = H$, $R_2 = C_7H_{15}$	TBDMS	$Pd_2(dba)_3$ / $P(OiPr)_3$	**14b**	0
3	**6b**	$R_1 = H$, $R_2 = C_7H_{15}$	TBDMS	$Pd_2(dba)_3$ / $P(OiPr)_3$ / **4Å MS**	**14b**	40
4	**6c**	$R_1 = H$, $R_2 = C_7H_{15}$	$PhMe_2Si$	$Pd_2(dba)_3$ / $P(OiPr)_3$	**14c**	0
5	**6c**	$R_1 = H$, $R_2 = C_7H_{15}$	$PhMe_2Si$	**$Pd(PPh_3)_4$**	**14c**	40

[a] C_6H_{11} refers to cyclohexyl and C_7H_{15} refers to *n*-heptyl. [b] P/Pd = 2/1; typically 40−80 mol % of Pd^0 was used. See experimental for details.

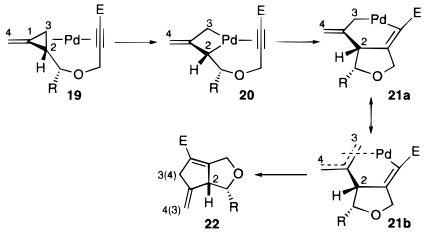
ular sieves were added (entry 3, Table 5) or when the catalyst was changed to $Pd(PPh_3)_4$ (entry 5, Table 5), were the cycloadducts obtained.[11] Even under these improved conditions a large amount of catalyst was required. It is not clear why molecular sieves lead to improved yields with some substrates beyond the obvious explanation of ensuring a dry reaction environment.

Although $Pd_2(dba)_3$ is the most popular source of Pd^0, the failure of certain substrates to undergo the cycloaddition and the difficulty of removing dba from the product prompted the initial studies with $Pd(PPh_3)_4$ described above. $Pd(PPh_3)_4$ is rarely used in the [3 + 2] MCP cycloaddition,[3a,6] although it is a popular catalyst in [3 + 2] TMM cycloadditions.[2] Our studies indicate $Pd(PPh_3)_4$ is a superior catalyst for many of the substrates described in this work. For example substrate **3e** underwent cycloaddition in 92% yield in the presence of 11 mol % $Pd(PPh_3)_4$, which is an increase of 40% compared to the corresponding $Pd_2(dba)_3$ reaction (entry 4, Table 4). Moderate improvement was also observed for a substrate bearing a carbomethoxy substituent (entry 5, Table 2). An added benefit of using $Pd(PPh_3)_4$ was that purification was much easier. A catalytic amount of $Pd(PPh_3)_4$ also catalyzed the cycloaddition of **10** and gave significantly less diene than $Pd_2(dba)_3$ (entry 4, Table 3).

Of the three catalytic systems studied, $Pd(PPh_3)_4$ exhibits the highest reactivity, but this catalyst is the most air-sensitive. Fortunately $Pd_2(dba)_3$ and $Pd_2(dba)_3$+sieves are satisfactory catalytic systems for many substrates. It is important to note that mixing $Pd_2(dba)_3$ with 4 equiv of PPh_3 did not give identical results to those obtained using $Pd(PPh_3)_4$. Furthermore the choice of catalyst appears to be much more crucial for the corresponding intramolecular [3 + 2] cycloaddition of MCP with *alkenes*.[12]

Investigation of the Mechanism of the Cycloaddition. In our preliminary report,[8] we proposed a sequence of events to explain the stereospecificity of the cycloaddition reaction (Scheme 1). The first step is probably coordination of the alkyne and the exocyclic methylene group to the palladium.[3a,13−16,17k] The metal then dissociates from the methylene moiety and coordinates to the cyclopropane in an edge-on orientation. Insertion into the distal cyclopropane bond generates a metallacyclobutane which undergoes carbometallation and reductive elimination to yield the observed cycloadduct. Since the overall reaction occurs with retention of configuration, an important issue was to determine if the reaction follows a retention−retention pathway or an inversion−inversion pathway in the key bond-breaking and bond-making steps.

Scheme 1



We see significant differences in reactivity as the substituent on the alkyne is varied which supports the notion that coordination of this group is an important step in the reaction pathway. Alkynes bearing electron-withdrawing groups are more reactive than those with a silicon, Tables 4 and 5.

During the cleavage of the cyclopropyl carbon−carbon bond trimethylenemethane−palladium complex of type **x** or metallacycle **y** have been proposed as intermediates. Both intermediates may even be possible depending on the catalyst and/or substrate.[14]

If the reaction goes through a TMM intermediate, a disrotatory-out ring-opening[17] where the 2,3-σ bond undergoing reaction bends away from the Pd^0 would lead to TMM complex **25a** (Scheme 2). The ensuing cycloaddition would then give cycloadduct **26** with net inversion of stereochemistry at C*. Our experimental results have unambiguously proven that cycload-

(11) (a) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(12) Lautens, M.; Ren, Y. *J. Am. Chem. Soc.*, in press.

(13) Simple η^2-coordination of metals with MCP has been observed for 1:1 complexes with Fe^0, Rh^{1+}, Ir^{1+}, Pt^{2+}, Pt^0, and Ni^0 in which the three-membered ring remains intact. See: (a) Green, M.; Howard, J. A. K.; Hughes, R. P.; Kellett, S. C.; Woodward, P. *J. Chem. Soc., Dalton Trans.* **1975**, 2007. (b) Whitesides, T. H.; Slaven, R. W. *J. Organomet. Chem.* **1974**, *67*, 99. (c) Slaven, R. W.; Calabrese, J. C. *Inorg. Chem.* **1974**, *13*, 1895. (d) Isaeva, L. S.; Peganova, T. A.; Petrovskii, P. V.; Kravtsov, D. N. *J. Organomet. Chem.* **1989**, *376*, 141. (e) Isaeva, L. S.; Peganova, T. A.; Petrovskii, P. V. *J. Organomet. Chem.* **1983**, *258*, 367. η^2-coordination of the alkyne, see: (f) Samsel, E. G.; Norton, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 5505. (g) Ryabov, A. D.; van Eldik, R.; Le Borgne, G.; Pfeffer, M. *Organometallics* **1993**, *12*, 1386. (h) de Vaal, P.; Dedieu, A. *J. Organomet. Chem.* **1994**, *478*, 121.

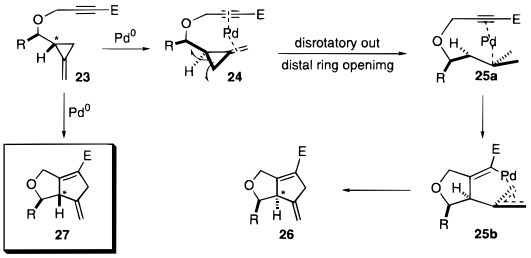
(14) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2326.

(15) Binger found that ligands such as maleic anhydride, acrolein, and acrylonitrile which bind very tightly to the catalyst can prevent any interaction of the metal with MCP, and thus inhibit the cycloaddition. See ref 3a.

(16) Binger found that intermolecular cycloaddition of MCP with simple unstrained alkenes is complicated by cyclodimerization of MCP rather than codimerization of MCP with alkenes due to the fact that MCP competes successfully with unactivated alkenes in π-complexation to the metal. This drawback can be overcome by simply using MCP substituted at the vinylic position to decrease the degree of π-complexation to the metal. See ref 3a.

(17) TMM−metal complexes from metal-induced disrotatory ring opening of alkylidenecyclopropanes are known. For the iron complex, see: (a) Noyori, R.; Nishimura, T.; Takaya, H. *J. Chem. Soc. D.* **1969**, 80. (b) Kagan, J.; Liu, W.-L.; Cohen, S. M.; Schwartz, R. N. *J. Organomet. Chem.* **1974**, *90*, 67. (c) Carpenter, B. K.; Pinhas, A. R. *J. Chem. Soc., Chem. Commun.* **1980**, 17. (d) Samuelson, A. G.; Carpenter, B. K. *J. Chem. Soc., Chem. Commun.* **1981**, 354. (e) Pinhas, A. R.; Samuelson, A. G.; Risemberg, R.; Arnold, E. V.; Clardy, J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 1668. For molybdenum complex, see: (f) Barnes, S. G.; Green, M. *J. Chem, Soc., Chem. Commun.* **1980**, 267. (g) Allen, S. R.; Barnes, S. G.; Green, M.; Moran, G.; Trollope, L.; Murrall, N. W.; Welch, A. J.; Sharaiha, D. M. *J. Chem, Soc. D.* **1984**, 1157. For $PdCl_2$ initiated disrotatory opening of MCP in chloropalladation reactions, see: (h) Clemens, P. R.; Hughes, R. P.; Martgerum, L. D. *J. Am. Chem. Soc.* **1981**, *103*, 2428. (i) Albright, T. A.; Clemens, P. R.; Hughes, R. P.; Hunton, D. E.; Martgerum, L. D. *J. Am. Chem. Soc.* **1982**, *104*, 5369. (j) Donaldson, W. A.; North, J. T.; Gruetzmacher, J. A.; Finley, M. *Tetrahedron* **1990**, *46*, 2263. For a theoretical calculation of Pd^0 initiated [3 + 2] cycloaddition of methylenecyclopropane with alkene, see: (k) Oishi, Y.; Sakamoto, E.; Fujimoto, H. *Inorg. Chem.* **1996**, *35*, 231.

Scheme 2



dition goes with overall retention of stereochemistry at C* indicating that TMM intermediates are not involved in the palladium catalyzed intramolecular cycloaddition with monosubstituted methylenecyclopropanes.

We found that with MCPs bearing methyl substituents at the angular position, insertion was followed by β-elimination to give dienes with alkyne tether intact (entry 3, Table 3). Motherwell also reported diene formation when methyl substituents were present at the angular position[6c] which suggest the existence of a distinct metallacyclobutane intermediate.

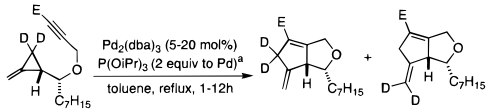
Insertion into a methylenecyclopropane ring can be achieved with a variety of different metals.[18] It has been shown that chloropalladation of MCP with a Pd^{2+} catalyst occurs with retention of stereochemistry.[19] Cross addition of platinum(II) hydride over MCP has also been found to occur with retention of configuration at the cyclopropane carbon.[20]

Bäckvall's theoretical study of the cyclopropane ring opening by Pd^0 and Pd^{2+} has shown that for Pd^0 only the edge activation has a low activation energy with a metallacyclobutane as the resulting complex.[21] The fate of the stereogenic carbon atom in a carbon−palladium complex upon reaction with an alkyne has been studied by Pfeffer who showed that retention of configuration occurred with the carbopalladation.[22] Since the stereochemistry at C-2 is retained in the pathway leading to the cycloadduct, a *double retention* pathway appears to be operating in the MCP cycloaddition.

In order to probe the nature of the intermediate, we prepared diastereomerically pure and/or deuterium labeled MCPs and subjected them to the reaction conditions. Deuterated methylenecyclopropane **28a** was prepared using a samarium mediated cyclopropanation of an allenic alcohol with CD_2I_2.[23] Reaction of **28a** with Pd^0 gave **29a** and **30a** with complete scrambling of the label at the vinylic and allylic positions as determined by ^1H and ^2H NMR (entry 1, Table 6). In our proposed mechanism, either metallacyclobutane **20** or metallacyclohexane **21a** can undergo interconversion between σ-allyl and π-allyl species, which exchanges C-3 and C-4 prior to reductive elimination to **22** (Scheme 1).

Interestingly, while scrambling of the carbon bearing the deuterium label was complete, scrambling of alkyls was not observed[6d] (entry 7, Table 2) which may be due to a steric effect.

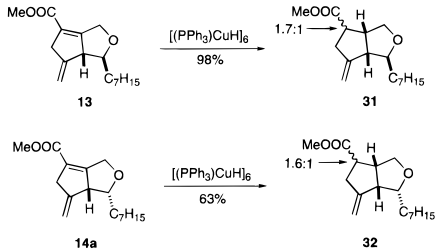
Table 6. Deuterium Labeling Studies



Entry	Substrate[b]	E	29 : 30 [c]	Yield (%) (29+30)	Recovered SM (%) (28)
1	**28a**	$COOCH_3$	1 : 1	72	0
2	**28a**	$COOCH_3$	1 : 1	18	78
3	**28b**	TMS	NA	0	82

[a] P/Pd = 2/1; typically 5−20 mol % of $Pd_2(dba)_3$ was used. See experimental for details. [b] C_7H_{15} refers to *n*-heptyl. [c] Ratio determined by ^1H and ^2H NMR.

Scheme 3



Two bulky substituents prefer to reside at C-4 of the exocyclic double bond in the metallacyclobutane (**20**, Scheme 1) and metallacyclohexane (**21a**, Scheme 1) rather than at C-3 in order to avoid steric-congestion with the bulky palladium−ligand complex.

When the reaction was run to 18% conversion, the recovered starting material showed no scrambling of the label between C-3 and C-4 but complete scrambling of label in the cycloadduct (entry 2, Table 6). This is in contrast to studies by Noyori using nickel catalysts where significant isomerization in the recovered methylenecyclopropane was observed.[2a,4e]

From these results, information on the relative rates of the various reaction processes in intramolecular palladium catalyzed cycloadditions can be obtained. Since no scrambling is observed in the recovered starting material, the insertion step must be irreversible and rapidly followed by carbometallation. Since complete scrambling is observed in the final product, the scrambling event must be faster than the final reductive elimination.

Reactions of the Cycloadducts. Selective 1,4-reduction of the enoate generates two new stereocenters and a product equivalent to the adduct from cycloaddition of an alkene. SmI_2 reduction[24] or an *in situ* generated copper hydride[25] led to decomposition, whereas the Stryker reagent[26] smoothly reacted with the enoate in high yield. The stereochemistry at angular carbon was fully controlled, but almost no selectivity was seen at the carbon bearing the ester (Scheme 3).

Similarly a methyl cuprate also added to the enoate.[27] The intermediate ketenesilylacetal **33** was remarkably stable to an aqueous workup and only decomposed to yield **34a** and **34b** during column chromatography. A quaternary carbon center

(18) (a) Phillips, R. L.; Puddephatt, R. G. *J. Chem. Soc. D*. **1978**, 1736. (b) Larock, R. C.; Varaprath, S. *J. Org. Chem.* **1984**, *49*, 3432. (c) Balme, G.; Fournet, G.; Gore, J. *Tetrahedron Lett.* **1986**, *27*, 3855. (d) Donaldson, W. A.; Brodt, C. A. *J. Organomet. Chem.* **1987**, *330*, C33. (e) Fournet, G.; Balme, G.; Gore, J. *Tetrahedron* **1988**, *44*, 5809. (f) Dallas, B. K.; Hughes, R. P.; Schumann, K. *J. Am. Chem. Soc.* **1982**, *104*, 5380. (g) Hughes, R. P.; Hunton, D. E.; Schumann, K. *J. Organomet. Chem.* **1980**, *184*, C67. (h) Noyori, R.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1969**, 77. Also see: refs 13(b) and 17(a), (e), (g), (h), (i), and (j).

(19) Green, M.; Hughes, R. P. *J. Chem. Soc. D*. **1976**, 1880.

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(23) For the preparation of dideuteriodiiodomethane, see: Winstein, S.; Friedrich, E. C.; Baker, R. and Lin, Y. *Tetrahedron Suppl.* **1966**, *8*, 621.

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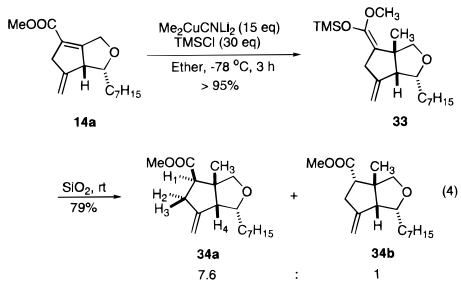
(25) Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. *J. Org. Chem.* **1977**, *42*, 3180.

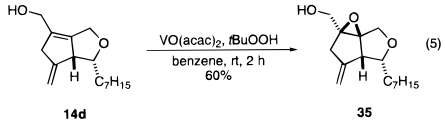
(26) (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291. (b) Koenig, T. M.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1989**, *30*, 5677. (c) Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M.*Tetrahedron Lett.* **1990**, *31*, 2397. (d) Mahoney, W. S.; Stryker, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8818.

(27) (a) Linderman, R. J.; Godfrey, A.; Horne, K. *Tetrahedron* **1989**, *45*, 495. (b) Linderman, R. J.; McKenzie, J. R. *J. Organomet. Chem.* **1989**, *361*, 31.

was created with complete stereochemical control, and good selectivity was also observed in the protonation step in contrast to the results described previously (eq 4). The stereochemistry of the major product **34a** was determined by NOE which showed that H_1 and H_2 were cis and H_3 and H_4 were on the same side as the newly introduced methyl group.



Selective epoxidation of the corresponding allylic alcohol **14d** was also possible using $VO(acac)_2$/*t*-BuOOH (eq 5).[28]



Summary

We have shown that palladium catalyzed intramolecular cycloaddition of diastereomerically pure methylenecyclopropanes is stereospecific and occurs with retention of configuration at the bond undergoing reaction. The reaction occurs in a stepwise fashion, and metallacycles are likely intermediates. We reacted deuterium labeled substrates and showed that insertion into the methylenecyclopropanes is irreversible. Three different types of palladium catalysts are found to facilitate the cycloaddition. We have explored the scope of the reaction and found that a wide range of substitution patterns in and around the reactive centers are tolerated. The stereospecificity does not seem to be affected by these changes. A few reactions of the cycloadduct have also been briefly investigated.

Experimental Section

The following includes general experimental procedures, specific details for representative reactions, and isolation and spectroscopic information for the compounds prepared.

General Procedure for the Propargylation. Potassium hydride (35 wt.% dispersion in mineral oil) was weighed in a flame-dried round bottomed flask and washed three times with dry pentane. The pentane residue was removed by blowing dry nitrogen through the flask for 5 min and the dry potassium hydride was weighed again. Dry THF was then added, and the solution was cooled to 0 °C. A solution of the methylenecyclopropane carbinol and a catalytic amount of 18-C-6 in THF were added slowly at 0 °C. The reaction mixture was stirred at 0 °C for 60 min prior to addition of propargyl bromide (80 wt % solution in toluene) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for another 2 h. The reaction was quenched by the addition of water. After a regular aqueous workup, the organic layer was dried over anhydrous $MgSO_4$. Purification by flash column chromatography, eluting with 2% ethyl acetate in hexanes provided the methylenecyclopropane carbinol propargyl ether.

General Procedure for the Carbomethoxylation. The propargyl ether was dissolved in THF and stirred at −78 °C. *n*-BuLi (2.5 M solution in hexane) was added slowly at −78 °C, and the resulting brown solution was stirred at −78 °C for 60 min. Methyl chloroformate was added at −78 °C, and the orange-brown solution was stirred at −78 °C for 1 h and then 2 h at room temperature. After an aqueous workup, flash column chromatography (2% ethyl acetate in hexanes) yielded the pure product.

General Procedure for the Cycloaddition using Pd^0. Procedure A: $Pd_2(dba)_3/P(OiPr)_3$. A flame-dried round bottomed flask, equipped with a condenser was charged with $Pd_2(dba)_3$ and $P(OiPr)_3$ (P/Pd = 2/1 in mol ratio). Toluene (desulfurized and freshly distilled over sodium) was introduced via a cannula followed by a solution of the substrate in toluene. The mixture was heated to 110 °C and stirred vigorously until the reaction was complete. Toluene was removed under vacuum and the crude mixture was purified by column chromatography. Elution of dibenzylideneacetone (dba) with toluene was followed by further elution using a mixture of ethyl acetate in hexanes to give the pure cycloadduct.

Procedure B: $Pd_2(dba)_3/P(OiPr)_3$/MS 4 Å. Identical to procedure A except 8−10 equiv (by weight vs $Pd_2(dba)_3$) of 4Å molecular sieves were added to the reaction flask containing $Pd_2(dba)_3$ and $P(OiPr)_3$.

Procedure C: $Pd(PPh_3)_4$. Identical to procedure A except $Pd(PPh_3)_4$ was added to the reaction flask instead of $Pd_2(dba)_3$ and $P(OiPr)_3$.

***cis*-1-Cyclohexyl-6-methylene-3,5,6,6a-tetrahydro-1*H*-cyclopenta-[*c*]furan-4-carboxylic Acid Methyl Ester (11a).** The cycloaddition was carried out as in general procedure A using **3a** (30 mg, 0.11 mmol) in toluene (25 mL) with $Pd_2(dba)_3$ (1.9 mg, 0.0021 mmol, 3.6 mol % of Pd^0) and $P(OiPr)_3$ (2.0 μL, 0.0081 mmol, 7.4 mol %). The yellow-brown reaction mixture was stirred at 110 °C for 1 h. The crude product was purified by flash column chromatography (using 2% ethyl acetate in hexanes as eluent) to afford **11a** (22.6 mg, 75%) as a colorless oil. IR (cm^{-1}, neat) 2935, 2870, 1724, 1442; ^1H NMR (400 MHz, $CDCl_3$) δ 4.93 (1H, m), 4.84 (1H, m), 4.56 (1H, ddd, J = 15.7, 4.4, 1.8 Hz), 4.40 (1H, dddd, J = 15.7, 4.4, 1.8, 1.8 Hz), 3.74 (1H, br d, J = 9.2 Hz), 3.71 (3H, s), 3.65 (1H, ddd, J = 19.2, 4.2, 2.5 Hz), 3.44−3.49 (2H, m), 1.87 (1H, dd, J = 12.8, 1.8 Hz), 1.76 (2H, m), 1.69 (2H, t, J = 12.1 Hz), 1.54 (1H, m), 1.09−1.28 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 164.1, 147.5, 122.7, 108.7, 84.7, 65.1, 57.8, 51.5, 44.4, 41.9, 30.2, 27.9, 26.6, 26.5, 26.2; HRMS calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1567.

***cis*-(1-Cyclohexyl-6-methylene-3,5,6,6a-tetrahydro-1*H*-cyclopenta[*c*]furan-4-yl)methanol (11b).** The cycloaddition was carried out as in general procedure A using **3b** (40 mg, 0.17 mmol) in toluene (40 mL) with $Pd_2(dba)_3$ (15.6 mg, 0.017 mmol, 20.0 mol % of Pd^0) and $P(OiPr)_3$ (17 μL, 0.068 mmol, 40 mol %). The yellow-brown reaction mixture was stirred at 110 °C for 4 h. The crude product was purified by flash column chromatography (using 5% ethyl acetate in hexanes as eluent) to afford **11b** (34 mg, 85%) as a colorless oil. IR (cm^{-1}, neat) 3400, 2940, 2872, 1718, 1659, 1456, 1012, 890, 738; ^1H NMR (400 MHz, $CDCl_3$) δ 4.90 (1H, dd, J = 3.7, 2.6 Hz), 4.82 (1H, dd, J = 4.1, 2.3 Hz), 4.36 (1H, d, J = 12.1 Hz), 4.12−4.22 (3H, m), 3.55−3.60 (1H, m), 3.51 (1H, br d, J = 19.0 Hz), 3.38 (1H, dd, J = 8.4, 5.1 Hz), 3.19 (1H, d, J = 19.0 Hz), 1.88 (1H, br d, J = 12.8 Hz), 1.77 (2H, br d, J = 10.6 Hz), 1.69 (2H, br t, J = 13.4 Hz), 1.46−1.56 (1H, m), 1.06−1.30 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 149.5, 143.4, 130.9, 107.7, 85.0, 63.1, 60.4, 56.3, 45.2, 42.3, 30.1, 28.2, 26.60, 26.59, 26.3; HRMS calcd for $C_{15}H_{22}O_2$ 234.3414, found 234.3417.

Cycloadduct **11b** was also prepared via the following procedure. DIBAL-H (0.6 mL, 1 M solution in hexane, 0.6 mmol) was added dropwise to a solution of **11a** (40 mg, 0.15 mmol) in THF (1 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h until TLC showed the reaction was complete. After an aqueous workup and drying of the organic layer over anhydrous $MgSO_4$, flash column chromatography (30% EtOAc in hexane) gave **11b** (35.5 mg, 99%) as a colorless oil.

Synthesis of Cycloadduct 11c. The cycloaddition was carried out as in general procedure A using **3c** (24 mg, 0.069 mmol) in toluene (15 mL) with $Pd_2(dba)_3$ (4.4 mg, 0.0048 mmol, 14.0 mol % of Pd^0) and $P(OiPr)_3$ (4.8 μL, 0.019 mmol, 28.0 mol %). The yellow-brown reaction mixture was stirred at 110 °C for 12 h. The crude product was purified by flash column chromatography (using 1% ethyl acetate in hexanes as eluent) to afford **11c** (24 mg, 100%) as a colorless oil. IR (cm^{-1}, neat) 2945, 2870, 1662, 1466, 1380, 1260, 1093, 840; ^1H NMR (400 MHz, $CDCl_3$) δ 4.87 (1H, d, J = 1.1 Hz), 4.80 (1H, d, J = 1.5 Hz), 4.40 (1H, d, J = 12.5 Hz), 4.18 (1H, s), 4.17 (1H, s), 4.15 (1H, ddd, J = 12.5, 4.0, 1.8 Hz), 3.50−3.57 (1H, m), 3.44 (1H, br d,

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J = 19.1 Hz), 3.36 (1H, dd, J = 8.4, 5.1 Hz), 3.10 (1H, d, J = 19.1 Hz), 1.88 (1H, br d, J = 11.7 Hz), 1.77 (2H, br d, J = 11.0 Hz), 1.68 (2H, br t, J = 13.9 Hz), 1.44−1.54 (1H, m), 1.04−1.30 (5H, m), 0.87 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 141.7, 131.0, 107.3, 84.8, 63.6, 61.2, 56.3, 45.2, 42.3, 30.3, 28.2, 26.64, 26.62, 26.3, 25.9, 18.3, −5.39, −5.43; HRMS calcd for $C_{21}H_{36}O_2Si$ 348.2484, found 348.2468.

***cis*-1-(1-Cyclohexyl-6-methylene-3,5,6,6a-tetrahydro-1*H*-cyclopenta-[*c*]furan-4-yl)ethanone (11e).** The cycloaddition was carried out as in general procedure C using **3e** (47 mg, 0.19 mmol) in toluene (30 mL) with $Pd(PPh_3)_4$ (25 mg, 0.022 mmol, 11 mol % of Pd^0). The yellow solution was stirred at 110 °C for 1.5 h. After removing the toluene, the crude product was purified by flash column chromatography (using 1−2% ethyl acetate in hexanes as eluent) to afford **11e** (43 mg, 92%) as a colorless oil. IR (cm^{-1}, neat) 3411, 2926, 2856, 1735, 1668, 1450, 1367, 1240, 1023; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (1H, dt, J = 4.1, 1.4 Hz), 4.84 (1H, dt, J = 3.7, 1.4 Hz), 4.57 (1H, ddd, J = 15.8, 4.8, 1.8 Hz), 4.48 (1H, dquint, J = 15.8, 1.8 Hz), 3.80 (1H, dquint, J = 9.2, 2.2 Hz), 3.65 (1H, ddt, J = 19.0, 6.6, 2.5 Hz), 3.45−3.54 (2H, m), 2.19 (3H, s), 1.87 (1H, br d, J = 12.4 Hz), 1.62−1.83 (4H, m), 1.50−1.60 (1H, m), 1.08−1.34 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 163.0, 147.1, 131.6, 108.5, 84.4, 65.4, 58.6, 44.6, 41.8, 30.2, 29.7, 28.9, 27.8, 26.5, 26.4, 26.2; HRMS calcd for $C_{16}H_{22}O_2$ 246.1620 , found 246.1621.

***cis*-3-Cyclohexyl-4-methylene-6-trimethylsilanyl-3,3a,4,5-tetrahydro-1*H*-cyclopenta[*c*]furan (11f).** The cycloaddition was carried out as in general procedure C using **3f** (50 mg, 0.18 mmol) in toluene (30 mL) with $Pd(PPh_3)_4$ (150 mg, 0.13 mmol, 72 mol % of Pd^0) added portionwise over 12 h. The yellow solution was stirred at 110 °C for 24 h. After removing of the toluene, the crude product was purified by flash column chromatography (using 10−30% toluene in hexanes as eluent) to afford **11f** (23 mg, 46%) as a colorless oil. IR (cm^{-1}, neat) 2926, 2855, 1723, 1663, 1452, 1250, 1026, 838; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (1H, s), 4.77 (1H, s), 4.22 (2H, br s), 3.56 (1H, br d, J = 8.8 Hz), 3.51 (1H, ddd, J = 18.7, 3.6, 2.5 Hz), 3.39 (1H, dd, J = 8.8, 5.5 Hz), 3.22 (1H, dt, J = 18.7, 1.5 Hz), 1.89 (1H, br d, J = 12.4 Hz), 1.60−1.82 (5H, m), 1.00−1.30 (5H, m), 0.067 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.3, 127.8, 125.5, 106.2, 84.8, 64.7, 57.9, 49.2, 42.5, 30.1, 28.3, 26.64, 26.63, 26.3, −1.3 (3C); HRMS calcd for $C_{17}H_{28}OSi$ 276.1909, found 276.1912.

***cis*-1-Cyclohexyl-3,5,6,6a-tetrahydro-6-methylene-1*H*-cyclopenta-[*c*]furan-4-methanol 3′,5′-Dinitrobenzote (11h).** 3,5-Dinitrobenzoic acid (43.5 mg, 0.21 mmol), 1,3-dicyclohexylcarbodiimide (DCC) (53 mg, 0.26 mmol), and 4-dimethylaminopyridine (DMAP) (4 mg, 0.033 mmol) were added to a solution of alcohol **11b** (40 mg, 0.17 mmol) in CH_2Cl_2 (2 mL). The yellow-brown solution was stirred at room temperature for 1 h until TLC indicated the reaction was complete. After an aqueous workup and drying of the organic layer over anhydrous $MgSO_4$, flash column chromatography (5% EtOAc in hexane) gave **11h** (68 mg, 93%) as a white solid. White crystalline needles were grown in a test tube from a 1:1 mixture of dichloromethane−pentane in a sealed container in the presence of water at 4 °C.

***trans*-1-Cyclohexyl-6-methylene-3,5,6,6a-tetrahydro-1*H*-cyclopenta[*c*]furan-4-carboxylic Acid Methyl Ester (12).** The cycloaddition was carried out as in general procedure A using **4** (40 mg, 0.15 mmol) in toluene (30 mL) with $Pd_2(dba)_3$ (7 mg, 0.0076 mmol, 10.0 mol % of Pd^0) and $P(OiPr)_3$ (7.5 μL, 0.030 mmol, 20 mol %). The yellow-brown reaction mixture was stirred at 110 °C for 1 h. The crude product was purified by flash column chromatography (using 2% ethyl acetate in hexanes as eluent) to afford **12** (28.6 mg, 72%) as a colorless oil. IR (cm^{-1}, neat) 2927, 2852, 1715, 1435, 1243, 1119; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (1H, dd, J = 5.1, 2.5 Hz), 4.93 (1H, dd, J = 5.1, 2.5 Hz), 4.60 (1H, ddd, J = 15.7, 4.0, 1.8 Hz), 4.39 (1H, dddd, J = 15.7, 3.6, 2.2, 2.2 Hz), 4.25 (1H, br d, J = 9.2 Hz), 4.06 (1H, dd, J = 9.2, 3.0 Hz), 3.73 (1H, br d, J = 20.5 Hz), 3.72 (3H, s), 3.62 (1H, ddd, J = 20.5, 1.8, 1.8 Hz), 1.70 (1H, dd, J = 12.4, 2.2 Hz), 1.46−1.66 (4H, m), 0.84−1.38 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 163.7, 144.6, 121.5, 110.3, 81.6, 65.7, 59.7, 51.6, 44.5, 39.9, 31.0, 26.8, 26.5, 26.2, 26.0; HRMS calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1562.

***cis*-1-Heptyl-6-methylene-3,5,6,6a-tetrahydro-1*H*-cyclopenta-[*c*]furan-4-carboxylic Acid Methyl Ester (13).** The cycloaddition was carried out as in general procedure A using **5** (22 mg, 0.079 mmol) in toluene (15 mL) with $Pd_2(dba)_3$ (8.3 mg, 0.0091 mmol, 23 mol % of Pd^0) and $P(OiPr)_3$ (5.7 μL, 0.023 mmol, 29 mol %). The yellow-brown reaction mixture was stirred at 110 °C for 1.5 h. The crude product was purified by flash column chromatography (using 2% ethyl acetate in hexanes as eluent) to afford **13** (15.6 mg, 71%) as a colorless oil. IR (cm^{-1}, neat) 2932, 2854, 1722, 1685, 1439, 1246, 1114; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (1H, dd, J = 3.7, 2.2 Hz), 4.86 (1H, dd, J = 4.4, 2.2 Hz), 4.55 (1H, ddd, J = 16.0, 4.4, 2.0 Hz), 4.46 (1H, dddd, J = 16.0, 4.0, 1.8, 1.8 Hz), 3.72 (3H, s), 3.45−3.73 (4H, m), 1.71−1.81 (1H, m), 1.59−1.69 (1H, m), 1.46−1.56 (1H, m), 1.36−1.46 (1H, m), 1.20−1.36 (8H, m), 0.86 (3H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 164.1, 146.4, 122.7, 108.4, 80.7, 65.4, 60.9, 51.5, 44.3, 35.2, 31.8, 29.7, 29.2, 26.1, 22.6, 14.1; HRMS calcd for $C_{17}H_{26}O_3$ 278.1882, found 278.1880.

***trans*-1-Heptyl-6-methylene-3,5,6,6a-tetrahydro-1*H*-cyclopenta-[*c*]furan-4-carboxylic Acid Methyl Ester (14a).** The cycloaddition was carried out as in general procedure A using **6a** (42 mg, 0.015 mmol) in toluene (20 mL) with $Pd_2(dba)_3$ (9.68 mg, 0.011 mmol, 14.0 mol % of Pd^0) and $P(OiPr)_3$ (10.4 μL, 0.042 mmol, 28.0 mol %). The yellow-brown reaction mixture was stirred at 110 °C for 1 h. After the workup, the crude product was purified by flash column chromatography (using 2% ethyl acetate in hexanes as eluent) to afford **14a** (29.5 mg, 70%) as a colorless oil. IR (cm^{-1}, neat) 2928, 2860, 1722, 1680, 1436, 1354, 1332, 1248, 1114, 1014; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (1H, d, J = 2.2 Hz), 4.83 (1H, d, J = 2.2 Hz), 4.51 (1H, dd, J = 16.1, 1.8 Hz), 4.38 (1H, ddd, J = 16.1, 1.8, 1.8 Hz), 4.21 (1H, d, J = 1.5 Hz), 4.20 (1H, d, J = 1.1 Hz), 3.72 (3H, s), 3.69 (1H, ddd, J = 20.5, 3.8, 2.7 Hz), 3.54 (1H, ddd, J = 20.5, 2.2, 1.8 Hz), 1.33−1.50 (2H, m), 1.24 (9H, br s), 1.06 (1H, br s), 0.85 (3H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 163.1, 144.6, 123.1, 110.5, 77.6, 63.6, 60.7, 51.5, 44.6, 31.8, 29.5, 29.32, 29.27, 25.8, 22.7, 14.1; HRMS calcd for $C_{17}H_{26}O_3$ 278.1882, found 278.1890.

***trans*-6-(*tert*-Butyldimethylsilanyl)-3-heptyl-4-methylene-3,3a,4,5-tetrahydro-1*H*-cyclopenta[*c*]furan (14b).** The cycloaddition was carried out as in general procedure B using **6b** (30 mg, 0.090 mmol) in toluene (30 mL) with portionwise addition of $Pd_2(dba)_3$ (40 mg, 0.044 mmol, 98 mol % of Pd^0), $P(OiPr)_3$ (0.045 μL, 0.18 mmol), and MS 4Å (200 mg). The yellow-brown reaction mixture was stirred at 110 °C for 12 h. After removal of the toluene, the crude product was purified by flash column chromatography (using 5−10% toluene in hexanes as eluent) to afford **14b** (11.8 mg, 40%) as a colorless oil. IR (cm^{-1}, neat) 2932, 2861, 1655, 1467, 1250, 1019, 976, 890, 837, 773; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (1H, br d, J = 2.2 Hz), 4.76 (1H, br d, J = 2.3 Hz), 4.18 (2H, br s), 4.12 (1H, dt, J = 2.4, 8.1 Hz), 4.04 (1H, br d, J = 7.7 Hz), 3.59 (1H, ddt, J = 20.1, 6.4, 2.7 Hz), 3.36 (1H, dt, J = 20.2, 1.8 Hz), 0.95−1.46 (15H, m), 0.87 (9H, s), 0.038 (3H, s), 0.034 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 148.4, 130.0, 107.9, 77.2, 63.6, 60.8, 51.3, 31.9, 29.75, 29.69, 29.3, 26.7 (3C), 25.8, 22.7, 17.8, 14.2, −5.4, −5.8; HRMS calcd for $C_{21}H_{38}OSi$ 334.2692, found 334.2680.

***trans*-6-(Dimethylphenylsilanyl)-3-heptyl-4-methylene-3,3a,4,5-tetrahydro-1*H*-cyclopenta[*c*]furan (14c).** The cycloaddition was carried out as in general procedure C using **6c** (48 mg, 0.14 mmol) in toluene (30 mL) with $Pd(PPh_3)_4$ (130 mg, 0.11 mmol, 78 mol % of Pd^0) added portion wise over 12 h. The yellow solution was stirred at 110 °C for 24 h. After removal of the toluene, the crude product was purified by flash column chromatography (using 10−20% toluene in hexanes as eluent) to afford **14c** (19 mg, 40%) as a colorless oil. IR (cm^{-1}, neat) 3073, 2961, 2929, 2854, 1661, 1640, 1463, 1426, 1249, 1110, 1014, 886, 832, 816, 773, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.48 (2H, m), 7.28−7.36 (3H, m), 4.97 (1H, br d, J = 2.2 Hz), 4.78 (1H, dd, J = 2.6, 1.8 Hz), 4.03−4.15 (3H, m), 3.98 (1H, br d, J = 14.3 Hz), 0.96−1.44 (12H, m), 0.86 (3H, t, J = 6.8 Hz), 0.35 (3H, s), 0.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 148.2, 137.7, 133.6 (2C), 129.8, 129.1, 127.8 (2C), 108.3, 77.6, 63.1, 61.0, 49.9, 31.9, 29.7 (2C), 29.3, 25.8, 22.7, 14.2, −2.4, −2.8; HRMS calcd for $C_{23}H_{33}OSi$ ($M - H^+$) 353.2301, found 353.2288.

Synthesis of Cycloadduct 15. The cycloaddition was carried out as in general procedure A using **7** (12.5 mg, 0.05 mmol) in toluene (15 mL) with $Pd_2(dba)_3$ (2.8 mg, 0.0031 mmol, 12.0 mol % of Pd^0) and $P(OiPr)_3$ (2.5 μL, 0.01 mmol, 20.1 mol %). The yellow-brown reaction mixture was stirred at 110 °C for 2h. The crude product was

purified by flash column chromatography (using 1% ethyl acetate in hexanes as eluent) to afford **15** (8.5 mg, 68%) as a colorless oil. IR (cm^{-1}, neat) 2933, 2862, 1716, 1682, 1439, 1241, 1111, 1006, 891, 770; ^1H NMR (500 MHz, $CDCl_3$) δ 5.07 (1H, dd, J = 4.9, 2.5 Hz), 4.93 (1H, dd, J = 4.9, 2.5 Hz), 4.52 (1H, ddd, J = 16.1, 4.4, 2.0 Hz), 4.43 (1H, ddt, J = 16.1, 3.9, 2.0 Hz), 3.74 (3H, s), 3.70 (1H, br d, J = 2.5 Hz), 3.68 (1H, ddd, J = 20.0, 3.9, 2.9 Hz), 3.53 (1H, dt, 20.0, 2.0 Hz), 1.80 (1H, br d, J = 12.2 Hz), 1.60−1.74 (3H, m), 1.48−1.59 (1H, m), 1.22−1.36 (3H, m), 1.10−1.20 (1H, m), 0.88 (1H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 164.2, 144.8, 123.0, 109.1, 81.3, 66.0, 63.3, 51.5, 44.5, 37.6, 28.1, 25.7, 22.9, 21.4; HRMS calcd for $C_{15}H_{19}O_3$ ($M\text{-}H^+$) 247.1334, found 247.1330.

***cis*-1-Cyclohexyl-6-(1-propylbutylidene)-3,5,6,6a-tetrahydro-1*H*-cyclopenta[*c*]furan-4-carboxylic Acid Methyl Ester (16).** The cycloaddition was carried out as in general procedure A using **8** (30 mg, 0.087 mmol) in toluene (20 mL) with $Pd_2(dba)_3$ (5.50 mg, 0.0061 mmol, 14.0 mol % of Pd^0) and $P(OiPr)_3$ (6.0 μL, 0.024 mmol, 28.0 mol %). The yellow-brown reaction mixture was stirred at 110 °C for 1.5 h. The crude product was purified by flash column chromatography (using 2% ethyl acetate in hexanes as eluent) to afford **16** (17.4 mg, 58%) as a colorless oil. IR (cm^{-1}, neat) 2923, 2863, 1723, 1600, 1455, 1432, 1243, 1121; ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 (1H, dd, J = 13.9, 1.5 Hz), 4.26 (1H, ddt, J = 13.9, 4.4, 1.5 Hz), 3.89 (1H, br d, J = 9.5 Hz), 3.73 (3H, s), 3.52 (2H, s), 3.39 (1H, dd, J = 9.5, 1.5 Hz), 1.14−2.00 (20H, m), 0.84−0.94 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 162.9, 137.5, 129.0, 124.2, 84.6, 64.3, 55.2, 51.4, 41.4, 39.9, 35.4, 34.6, 31.7, 27.0, 26.5, 26.3, 24.6, 21.8, 20.8, 14.2, 14.1; HRMS calcd for $C_{22}H_{34}O_3$ 346.2508, found 346.2491.

***cis*-1-Cyclohexyl-6a-methoxy-6-methylene-3,5,6,6a-tetrahydro-1*H*-cyclopenta[*c*]furan-4-carboxylic Acid Methyl Ester (17).** The cycloaddition was carried out as in general procedure A using **9** (40 mg, 0.14 mmol) in toluene (30 mL) with $Pd_2(dba)_3$ (8.78 mg, 0.0096 mmol, 14.0 mol % of Pd^0) and $P(OiPr)_3$ (9.5 μL, 0.038 mmol, 28.0 mol %). The yellow-brown reaction mixture was stirred at 80 °C for 12 h. The crude product was purified by flash column chromatography (using 2% ethyl acetate in hexanes as eluent) to afford **17** (30.0 mg, 75%) as a colorless oil. IR (cm^{-1}, neat) 2930, 2862, 1726, 1448; ^1H NMR (400 MHz, $CDCl_3$) δ 5.39 (2H, m), 4.59 (1H, ddd, J = 14.6, 2.2, 1.8 Hz), 4.39 (1H, ddd, J = 14.6, 4.0, 2.9 Hz), 3.76 (3H, s), 3.55 (1H, ddd, J = 20.5, 4.0, 2.2 Hz), 3.48 (1H, ddd, J = 20.5, 2.6, 1.8 Hz), 3.34 (1H, d, J = 7.7 Hz), 3.16 (3H, s), 2.07 (1H, br d, J = 13.2 Hz), 1.82−1.96 (2H, m), 1.71 (2H, br d, J = 13.2 Hz), 1.64 (1H, br d, J = 12.1 Hz), 0.98−1.31 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 159.6, 143.3, 127.2, 115.8, 94.4, 86.7, 63.5, 51.9, 51.3, 42.9, 38.2, 30.5, 30.4, 26.5, 26.2, 26.1; HRMS calcd for $C_{17}H_{25}O_4$ (MH^+) 293.1753, found 293.1762.

***cis*-1-Cyclohexyl-6a-methyl-6-methylene-3,5,6,6a-tetrahydro-1*H*-cyclopenta[*c*]furan-4-carboxylic Acid Methyl Ester (18).** The cycloaddition was carried out as in general procedure C using **10** (30 mg, 0.11 mmol) in toluene (30 mL) with $Pd(PPh_3)_4$ (15 mg, 0.013 mmol, 12 mol % of Pd^0). The yellow solution was stirred at 110 °C for 4 h. The crude product was purified by flash column chromatography (using 0−2% EtOAc in toluene as eluent) to afford **18** (13 mg, 43%) as a colorless oil. IR (cm^{-1}, neat) 2924, 2855, 1720, 1693, 1444, 1348, 1333, 1237, 1115, 1020, 887; ^1H NMR (400 MHz, $CDCl_3$) δ 4.92 (1H, dd, J = 2.6, 1.1 Hz), 4.90 (1H, dd, J = 2.2, 1.1 Hz), 4.51 (1H, ddd, J = 16.5, 2.9, 1.8 Hz), 4.43 (1H, ddd, J = 16.5, 4.2, 2.0 Hz), 3.73 (1H, br d, J = 19.0 Hz), 3.71 (3H, s), 3.41 (1H, br d, J = 19.0 Hz), 3.33 (1H, d, J = 3.3 Hz), 2.08 (1H, br d, J = 14.6 Hz), 1.40−1.80 (2H, m), 1.22 (3H, s), 0.98−1.36 (3H, m), 0.80−0.90 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 165.0, 152.3, 120.8, 108.8, 86.5, 63.8, 61.8, 51.6, 43.2, 39.3, 31.0, 30.6, 26.5, 26.2, 26.0, 18.4; HRMS calcd for $C_{17}H_{24}O_3$ 276.1725, found 276.1731.

***cis*-(1-Cyclohexyl-6a-methyl-6-methylene-3,5,6,6a-tetrahydro-1*H*-cyclopenta[*c*]furan-4-yl)methanol (18a). 18** was then reduced to the corresponding alcohols **18a** by treating with Dabal-H in THF at −78 °C. For compounds **18a**: IR (cm^{-1}, neat) 3387, 2923, 2852, 1657, 1448, 1376, 1043, 1007, 887, 737; ^1H NMR (400 MHz, $CDCl_3$) δ 4.91 (1H, dd, J = 2.7, 1.5 Hz), 4.88 (1H, dd, J = 2.1, 1.5 Hz), 4.29 (1H, dd, J = 12.5, 1.0 Hz), 4.21 (1H, ddt, J = 12.5, 6.1, 1.8 Hz), 4.18 (1H, d, J = 13.7 Hz), 4.13 (1H, d, J = 13.7 Hz), 3.56 (1H, br d, J = 18.9 Hz), 3.24 (1H, d, J = 8.9 Hz), 3.16 (1H, d, J = 18.9 Hz), 2.06 (1H, br d, J = 12.8 Hz), 1.69−1.84 (2H, m), 1.60−1.69 (1H, m), 1.40−1.58 (1H, m), 1.10−1.34 (3H, m), 1.16 (3H, s), 0.93−1.09 (2H, m), 0.80−0.92 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 148.7, 128.8, 108.0, 86.7, 61.6, 60.4, 60.0, 44.1, 39.6, 31.0, 30.6, 26.5, 26.2, 26.0, 18.5.

(*R*,S)-4-[1-(3-Methylenecyclopropyl-2,2-d_2)-octyloxy]but-2-ynoic Acid Methyl Ester (28a).** The carbomethoxylation was carried out as in the general procedure. *n*-BuLi (2.5 M solution in hexane, 0.18 mL, 0.45 mmol) was added to the propargyl ether (90 mg, 0.40 mmol) in THF (2 mL), followed by methyl chloroformate (0.062 mL, 0.81 mmol) to give **28a** (92 mg, 81%) as a colorless oil. IR (cm^{-1}, neat) 2955, 2925, 2857, 2242, 1720, 1433, 1381, 1255, 1090, 1057, 892, 751; ^1H NMR (400 MHz, $CDCl_3$) δ 5.47 (2H, m), 4.43 (1H, d, J = 16.7 Hz), 4.35 (1H, d, J = 16.7 Hz), 3.77 (3H, s), 2.96 (1H, dt, J = 8.4, 6.2 Hz), 1.60−1.66 (2H, m), 1.44−1.54 (2H, m), 1.34−1.44 (1H, m), 1.28 (8H, br s), 0.88 (3H, t, J = 6.7 Hz); ^2H NMR (61 MHz, $CHCl_3$) δ 1.26 (1D, s), 0.81 (1D, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 133.5, 104.6, 84.7, 82.0, 77.1, 55.8, 52.7, 35.0, 31.8, 29.6, 29.3, 25.5, 22.7, 19.1, 14.1, 6.5 (m); HRMS calcd for $C_{17}H_{25}D_2O_3$ 281.2086 (MH^+), found 281.2082.

***trans*-1-Heptyl-6-methylene-3,5,6,6a-tetrahydro-5-*d*-1*H*-cyclopenta[*c*]furan-5-*d*-4-carboxylic Acid Methyl Ester (29a)** and ***trans*-1-Heptyl-6-(methylene-d_2)-3,5,6,6a-tetrahydro-1*H*-cyclopenta[*c*]furan-4-carboxylic Acid Methyl Ester (30a).** The cycloaddition was carried out as in general procedure A using **28a** (54 mg, 0.193 mmol) in toluene (30 mL) with $Pd_2(dba)_3$ (8.80 mg, 0.0096 mmol, 10 mol % of Pd^0) and $P(OiPr)_3$ (9.4 μL, 0.038 mmol, 20.0 mol %). The yellow-brown reaction mixture was stirred at 110 °C for 7 h. The crude product was purified by flash column chromatography (using 2% ethyl acetate in hexanes as eluent) to afford a 1:1 mixture of **29a** and **30a** (39.1 mg, 72% combined yield) as a colorless oil. IR (cm^{-1}, neat) 2955, 2927, 2860, 1722, 1683, 1458, 1437, 1352, 1328, 1277, 1245, 1203, 1164, 1116, 1012, 901, 762, 710; ^1H NMR (400 MHz, $CDCl_3$) δ 5.08 (1H, d, J = 2.6 Hz), 4.84 (1H, d, J = 1.8 Hz), 4.51 (2H, d, J = 15.9 Hz), 4.38 (2H, d, J = 15.9 Hz), 4.22 (2H, s), 4.20 (2H, s), 3.72 (6H, s), 3.69 (1H, ddd, J = 20.3, 3.7, 2.5 Hz), 3.54 (1H, dt, J = 20.3, 2.0 Hz), 1.33−1.50 (4H, m), 1.24 (18H, br s), 1.06 (2H, br s), 0.85 (6H, t, J = 6.8 Hz); ^2H NMR (61 MHz, $CHCl_3$) δ 5.10 (1D, s), 4.86 (1D, s), 3.68 (1D, s), 3.54 (1D, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.58, 164.56, 163.29, 163.16, 144.52, 144.39, 123.11, 123.00, 110.53, 110.48, 109.9 (m), 77.59, 63.54, 60.67, 60.61, 51.53, 44.50, 44.0 (m), 31.83, 29.52, 29.32, 29.24, 25.78, 22.66, 14.12; HRMS calcd for $C_{17}H_{24}D_2O_3$ 280.2007, found 280.2001.

Incomplete Cycloaddition of 28a. The cycloaddition was carried out as in general procedure A using **28a** (50 mg, 0.18 mmol) in toluene (25 mL) with $Pd_2(dba)_3$ (4.9 mg, 0.0054 mmol, 6 mol % of Pd^0) and $P(OiPr)_3$ (5.3 μL, 0.021 mmol, 12 mol %). The yellow-brown reaction mixture was stirred at 110 °C for 50 min. The crude product was purified by flash column chromatography (using 2% ethyl acetate in hexanes as eluent) to afford starting material **28a** (39 mg, 78%) and cycloadducts **29a** and **30a** (8.8 mg, 18%). ^2H NMR of the mixture of **29a** and **30a** indicated complete scrambling between C-1 and C-3, whereas ^2H NMR of **28a** showed no scrambling of deuterium in the recovered starting material.

(*R*,S)-1-Methylene-2-[1-(3-trimethylsilanylprop-2-ynyloxy)octyl]-3,3-d_2-cyclopropane (28b).** The deprotonation was carried out as described in the general procedure for carbomethoxylation. Freshly distilled TMSCl (0.1 mL, 0.79 mmol) was added to a solution of the alkyne (65 mg, 0.29 mmol) and MeLi (1.4 M solution in ether, 0.22 mL, 0.31 mmol) at −78 °C. The resulting mixture was stirred at −78 °C for 1 h and room temperature for 2 h. Aqueous workup and column chromatography gave compound **28b** (80 mg, 93%). IR (cm^{-1}, neat) 3071, 2958, 2928, 2856, 2173, 1462, 1378, 1346, 1251, 1084, 994, 888, 845, 761; ^1H NMR (400 MHz, $CDCl_3$) δ 5.47 (1H, d, J = 0.7 Hz), 5.43 (1H, d, J = 2.2 Hz), 4.29 (1H, d, J = 15.7 Hz), 4.15 (1H, d, J = 15.7 Hz), 2.94 (1H, dt, J = 8.8, 6.0 Hz), 1.56−1.64 (2H, m), 1.42−1.54 (2H, m), 1.30−1.40 (1H, m), 1.26 (8H, br s), 0.86 (3H, t, J = 6.7 Hz), 0.15 (9H, s); ^2H NMR (61 MHz, $CHCl_3$) δ 1.23 (1D, s), 0.80 (1D, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.7, 104.3, 102.5, 90.4, 81.3, 57.0, 35.0, 31.9, 29.7, 29.3, 25.7, 22.7, 19.4, 14.1, 6.2 (1C, br qn), −0.1 (3C).

Cycloaddition of 28b. The cycloaddition was carried out as in general procedure A using **28b** (60 mg, 0.20 mmol) in toluene (30 mL) with $Pd_2(dba)_3$ (19.3 mg, 0.021 mmol, 20.7 mol % of Pd^0) and $P(OiPr)_3$ (20 μL, 0.081 mmol, 40 mol %). The brown-black solution was stirred at 110 °C for 24 h. The crude product was purified by flash column chromatography (using 1% ethyl acetate in hexanes as eluent) to recover starting material **28b** (49 mg, 82%). ^{2}H NMR of **28b** showed no scrambling of deuterium.

General Procedure for Reaction of the Cycloadducts with Stryker's Reagent. THF and H_2O were degassed by sparging with argon gas for 20 min. Stryker's reagent in THF was added to a mixture of the cycloadduct in THF and H_2O, and the mixture was stirred at room temperature for 2 h. The solvent was removed, and the residue was purified by column chromatography.

[1α,3aα,4α(or*β*),6aα]-(±)-1-Heptyl-6-methylenehexahydrocyclopenta[c]furan-4-carboxylic Acid Methyl Ester (31). Hydride addition was carried out as described in the general procedure, using cycloadduct **13** (23 mg, 0.083 mmol) in THF (4 mL) with H_2O (20 μL) and Stryker's reagent (200 mg, 0.10 mmol) to yield **31** (22.7 mg, 98%) as an inseparable 1.7:1 mixture of epimers.

[1α,3aα,4α(or*β*),6aα]-(±)-(1-Heptyl-6-methylenehexahydrocyclopenta[c]furan-4-yl)methanol (31a). 31 was then reduced to the corresponding alcohols **31a** by treating with Dabal-H in THF at −78 °C. For compounds **31a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (2H, br s), 4.82 (1H, dd, J = 2.2, 1.5 Hz), 4.79 (1H, dd, J = 2.6, 1.5 Hz), 4.08 (1H, dd, J = 8.8, 7.3 Hz), 3.93 (1H, dd, J = 9.2, 7.7 Hz), 3.67 (1H, dd, J = 10.6, 6.2 Hz), 3.62 (1H, dd, J = 10.6, 7.0 Hz), 3.44−3.56 (6H, m), 2.87 (1H, quintet, J = 8.0 Hz), 2.70−2.76 (1H, m), 2.64−2.70 (1H, m), 2.55−2.63 (2H, m), 2.16−2.39 (4H, m), 1.99 (1H, d, J = 3.7 Hz), 1.16−1.64 (12H, m), 0.86 (3H, t, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 152.5, 107.4, 107.0, 86.7, 85.9, 72.8, 67.7, 65.8, 63.7, 55.6, 54.9, 47.9, 46.2, 44.9, 43.0, 35.9, 35.4, 35.1, 35.0, 31.8, 29.73, 29.70, 29.3, 26.46, 26.38, 22.7, 14.1.

[1*β*,3aα,4α(or*β*),6aα]-(±)-1-Heptyl-6-methylenehexahydrocyclopenta[c]furan-4-carboxylic Acid Methyl Ester (32). Hydride addition was carried out as described in the general procedure, using cycloadduct **14a** (30 mg, 0.11 mmol) in THF (4 mL) with H_2O (19 μL) and Stryker's reagent (200 mg, 0.10 mmol) to yield **32** (19 mg, 63%) as an inseparable 1.6:1 mixture of epimers.

[1*β*,3aα,4α(or*β*),6aα]-(±)-(1-Heptyl-6-methylenehexahydrocyclopenta[c]furan-4-yl)methanol (32a). **32** was then reduced to the corresponding alcohols **32a** by treating with Dabal-H in THF at −78 °C. For compounds **32a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (1H, dd, J = 2.5, 1.1 Hz), 4.96 (1H, d, J = 1.1 Hz), 4.77 (1H, d, J = 1.5 Hz), 4.71 (1H, t, J = 1.1 Hz), 4.02 (1H, dd, J = 9.9, 1.8 Hz), 3.79 (1H, d, J = 6.6 Hz), 3.76 (1H, d, J = 6.6 Hz), 3.69 (1H, t, J = 7.7 Hz), 3.58−3.64 (2H, m), 3.54 (1H, d, J = 7.4 Hz), 3.52 (1H, d, J = 7.3 Hz), 3.40 (2H, d, J = 7.4 Hz), 3.00 (1H, t, J = 7.7 Hz), 2.92 (1H, t, J = 7.3 Hz), 2.89 (1H, t, J = 7.0 Hz), 2.60 (1H, t, J = 7.1 Hz), 2.39 (1H, ddd, J = 15.1, 7.7, 1.5 Hz), 2.23 (1H, d, J = 6.2 Hz), 2.19 (1H, d, J = 6.6 Hz), 2.09 (1H, d, J = 15.0 Hz), 2.03 (1H, dd, J = 15.1, 7.7 Hz), 1.90 (1H, dt, J = 1.5, 14.6 Hz), 1.58 (1H, s), 1.18−1.54 (12H, m), 0.86 (3H, t, J = 6.6 Hz).

[1*β*,3aα,4α,6aα]-(±)-1-Heptyl-3a-methyl-6-methylenehexahydrocyclopenta[c]furan-4-carboxylic Acid Methyl Ester (34a). To a solution of CuCN (148 mg, 1.65 mmol) in ether (2 mL) at −78 °C was added MeLi (2.35 mL, 3.3 mmol). The mixture was warmed to 0 °C, stirred for 5 min and then recooled to −78 °C. A solution of **14a** (30 mg, 0.11 mmol) in ether (3 mL) at −78 °C was added slowly to the cuprate solution via a cannula followed by addition of TMSCl (0.4 mL, 3.3 mmol) at −78 °C. The mixture was kept at −78 °C for 3 h and warmed up to −50 °C for 30 min. The reaction was quenched by adding a solution of NH_4Cl-NH_4OH (2:1) at −78 °C. The reaction was exposed to air and stirred until the color changed from yellow to blue. Standard workup yielded **33** (^{1}H NMR of crude mixture is essentially pure **33**). Column chromatography on silica gel using 2−4% EtOAc in hexanes provided **34** (25 mg, 79%) as an inseparable mixture of two isomers in a 7.6 : 1 ratio in favor of **34a**. For compound **34a**: IR (cm^{-1}, neat) 3076, 2957, 2926, 2854, 1737, 1660, 1459, 1434, 1362, 1254, 1233, 1197, 1166, 1058, 888; ^{1}H NMR (400 MHz, C_6D_6) δ 4.94 (1H, d, J = 1.4 Hz), 4.63 (1H, t, J = 1.1 Hz), 4.16 (1H, d, J = 9.9 Hz), 3.64−3.68 (1H, m), 3.32 (1H, dd, J = 9.9, 1.1 Hz), 3.26 (3H, s), 2.91 (1H, br t, J = 14.5 Hz), 2.47 (1H, ddd, J = 13.2, 6.6, 1.1 Hz), 2.33 (1H, dd, J = 14.6, 6.6 Hz), 2.25 (1H, br d, J = 5.9 Hz), 1.55−1.75 (2H, m), 1.14−1.54 (10H, m), 1.24 (3H, s), 0.89 (3H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 148.1, 109.2, 82.5, 76.4, 60.4, 53.8, 53.4, 51.6, 38.2, 31.8, 30.8, 29.7, 29.3, 27.0, 25.7, 22.7, 14.1; HRMS calcd for $C_{18}H_{31}O_3$ (MH^+) 295.2273, found 295.2279.

[1aα,3a*β*,4α,6aS*]-(±)-(4-Heptyl-3-methylenetetrahydro-1,5-dioxacyclopropa[c]pentalen-1a-yl)methanol (35). To allylic alcohol **14d** (25 mg, 0.10 mmol) in anhydrous benzene (1 mL) was added $VO(acac)_2$ (5 mg, 0.019 mmol) followed by *t*-BuOOH (0.015 mL, 0.15 mmol). The resulting brown solution was stirred at room temperature for 1 h. Saturated $Na_2S_2O_3$ solution was added to quench the reaction. Normal workup and column chromatography (20−30% EtOAc in hexanes) afforded epoxide **35** (16 mg, 60%). IR (cm^{-1}, neat) 3432, 3077, 2936, 2862, 2246, 1656, 1468, 1415, 1381, 1019, 912, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (1H, dd, J = 3.6, 2.0 Hz), 4.96−4.98 (1H, m), 4.17 (1H, br t, J = 9.6 Hz), 3.87−3.94 (3H, m), 3.81 (1H, br d, J = 12.8 Hz), 3.36 (1H, d, J = 8.5 Hz), 2.79 (1H, d, J = 18.3 Hz), 2.66 (1H, ddd, J = 18.3, 4.8, 2.6 Hz), 1.81 (1H, br s), 1.10−1.52 (12 H, m), 0.85 (3H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 114.0, 80.0, 70.6, 60.9, 60.7, 52.7, 37.7, 31.8, 30.4, 29.4, 29.2, 26.1, 22.65, 22.63, 14.1; HRMS calcd for $C_{16}H_{26}O_3$ 266.1882, found 266.1876.

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Supporting Information Available: Text describing the details of experimental procedures and compound characterization data that are not included in the Experimental Section (10 pages). See any current masthead page for ordering and Internet access instructions.

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