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RCM for the Construction of Novel Steroid-like Polycyclic Systems. 1. Studies on the Synthesis of a PreD$_3$-D$_3$ Transition State Analogue‡

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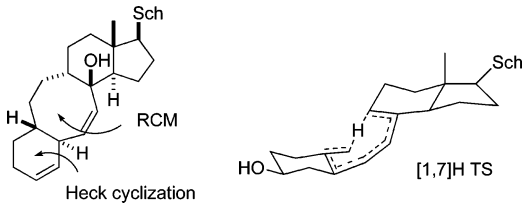

Natural and nonnatural polycyclic systems containing eight-membered carbocycles constitute a large class of compounds of importance in organic chemistry, biology, and medicine. Here we describe a new strategy by which complex polycyclic steroid-like systems can be constructed on the steroid CD framework, by a combination of RCM and Heck cyclizations. The method is exemplified by its application to the stereoselective synthesis of 6-8-6 fused carbocyclic systems that mimic the putative transition structure of the isomerization of previtamin D$_3$ to vitamin D$_3$.

Introduction

Steroids constitute an extensive and important class of biologically active polycyclic compounds that are widely used for therapeutic purposes.[1] Many functional and structural modifications of steroids have recently been investigated in order to extend their already broad range of biological activities and to increase their selectivity. In this article we describe our results on the preparation of novel steroid-like compounds containing an eight-membered B ring. Medium-sized carbocycles, particularly eight-membered ones, constitute the structural core of a large number of biologically important natural and nonnatural products.[2] The difficulty in constructing rings of this size by conventional cyclization routes is due to well-understood unfavorable entropic and enthalpic factors,[3] making their preparation a great synthetic challenge. However, in this respect transition-metal-catalyzed reactions have proven to be versatile tools both for construction of the steroid skeleton from easily available building blocks,[4] and for its functionalization;[5] and within the repertoire of transition-metal-catalyzed reactions, ring-closing metathesis (RCM) has become one of the most powerful tools for the construction of a variety of cyclic structures that would be difficult to achieve with

‡ This paper is dedicated to Prof. Pierre Potier in honor of his 70th birthday.

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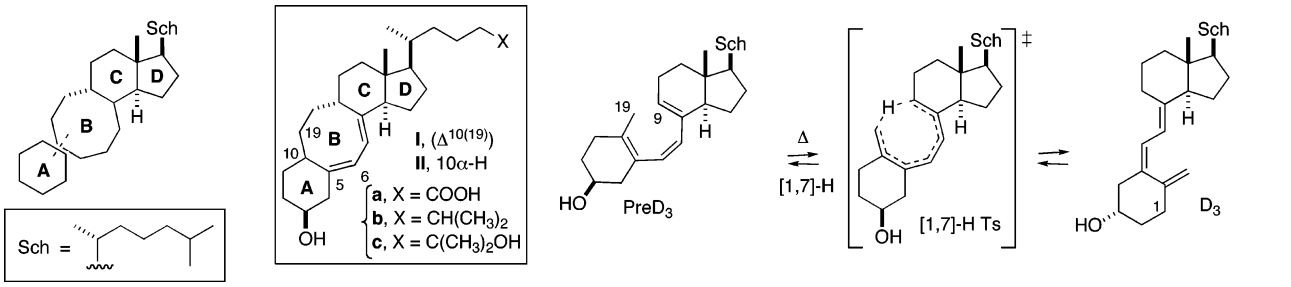

FIGURE 1. General structure of novel steroid-like compounds containing an eight-membered ring B, and the structures of [1,7]-H Ts analogues **I** and **II** and the putative mechanism of the [1,7] sigmatropic hydrogen shift of preD$_3$-D$_3$ isomerization.

other methods.[6] In particular, despite the above-mentioned unfavorable thermodynamic factors, olefin RCM has been successfully applied to the synthesis of eight-membered rings, though only when the substrate has some feature, such as conformation-constraining, preexisting rings or a polar group, that facilitates deployment of the reaction sites within the coordination sphere of the metal.[7,8] In the work described in this article, we constructed steroid-like polycycles with a linearly fused 6-8-6 carbocyclic system (**I** and **II**, Figure 1) by combining RCM (used to form ring B or a 12-membered precursor) with another of the most powerful transition-metal-catalyzed processes: the intramolecular Heck[9] reaction (used to form the six-membered ring A).[10] These synthetic targets mimic [1,7]-H Ts, the putative cyclic transition state of the isomerization[11,12] of previtamin D$_3$ (preD$_3$) to vitamin D$_3$ (D$_3$);[13] our hope is that antibodies raised against compounds of this type may catalyze this isomerization process, and that understanding of its mechanism may be furthered by the study of the active sites of such antibodies.[14] As locked 6-*s*-*cis* analogues of 1α,25-(OH)$_2$-D$_3$,[15−17] vitamin D derivatives with this central eight-membered ring might also be useful for studying nongenomic responses to vitamin D.

Results and Discussion

Our initial target was the preparation of compounds **1** (Figure 2). Initially, we designed three synthetic strategies for the preparation of its basic carbon framework. In all three, the C5−C6[18] double bond would be incorporated in ring B or in a 12-membered precursor carbocycle by a RCM reaction of a diene precursor formed by α-alkylation of the kinetic enolate of ketone **2** followed by allylation of the carbonyl carbon. In path A, the RCM reaction would form the eight-membered ring in a substrate in which the six-membered ring A would be present already. The six-membered ring of the precursor of the alkylating agent **4** would be formed by a Heck[9]

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(10) For some examples of sequential RCM/Heck reactions, see: Grigg, R.; Sridharan, V.; York, M. *Tetrahderon Lett.* **1998**, *39*, 4139−4142. Grigg, R.; York, M. *Tetrahderon Lett.* **2000**, *41*, 7255−7258.

(11) This isomerization, one of two successive pericyclic reactions in the photobiogenesis of vitamin D$_3$ (Figure 1),[12] consists of a thermally induced antarafacial [1,7]-sigmatropic hydrogen shift from C19 to C9. For studies of the mechanism of this physiologically important transformation, see: (a) Havinga, E. *Experientia* **1973**, *29*, 1181−1192. (b) Okamura, W. H.; Midland, M. M.; Hammond, M. W.; Rahman, N. A.; Dormanen, M. C.; Nemere, I.; Norman, A. W. *J. Steroid Biochem. Mol. Biol.* **1995**, *53*, 603−613. (c) Tian, X. Q.; Holick, M. F. *J. Biol. Chem.* **1999**, *274*, 4174−4179.

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(15) The biological functions of the hormonally active form of D$_3$, 1α,25-dihydroxyvitamin D$_3$,[16] are now thought to include promotion of cell differentiation, inhibition of tumor cell proliferation, and induction of functions related to the immunological system. For some studies of the biological activity of this hormone, see: (a) Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocr. Rev*. **1995**, *16*, 200−257. (b) *Vitamin D*: *Chemistry*, *Biology and Clinical Applications of the Steroid Hormone*; Norman, A. W., Bouillon, R., Thomasset, M., Eds; Vitamin D Workshop, Inc.; Riverside, CA, 1997.

(16) The involvement of a preD$_3$ ⇄ D$_3$-type equilibrium in nongenomic activities is hinted at by experimental results suggesting that these activities are mediated by membrane receptors for 1α,25-(OH)$_2$-PreD$_3$ as well as by 1α,25-(OH)$_2$-D$_3$, see: (a) Norman, A. W.; Okamura, W. H.; Farach-Carson, M. C.; Allewaert, K.; Branisteanu, D.; Nemere, I.; Muralidharan, K. R.; Bouillon, R. *J. Biol. Chem.* **1993**, *268*, 13811−13819. (b) Okamura, W. H.; Midland, M. M.; Norman, A. W.; Hammond, M. W.; Rahman, N. A.; Dormanen, M. C.; Nemere, I. *Ann. N.Y. Acad. Sci.* **1995**, *761*, 344−348.

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(18) For convenience, steroid numbering is used.

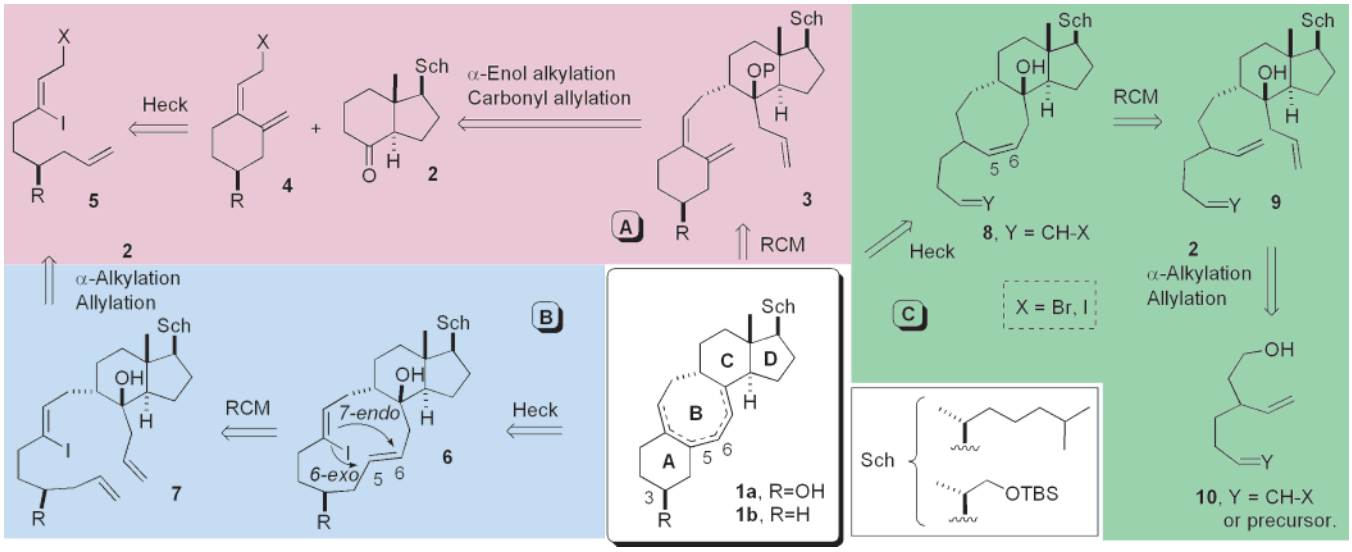
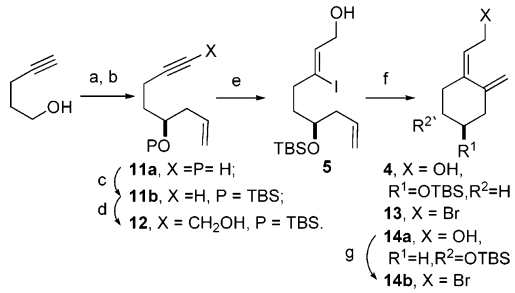


FIGURE 2. Proposed strategies for preparation of compounds **1**.

SCHEME 1. Preparation of Compounds 4, 5, and 14b[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N; (b) (i) (*R*)-Binol/Ti(OiPr)$_4$, CH_2Cl_2, (ii) $CH_2CHCH_2SnBu_3$, Δ, 81% (from 4-pentynol); (c) TBSCl, Im, DMF, 92%; (d) *n*BuLi, $(CH_2O)_n$, 91%; (e) Red-Al, I_2, 70%; (f) $(Ph_3P)_4Pd$, Et_3N, CH_3CN, 85%; (g) CBr_4, Ph_3P, CH_2Cl_2, 81%.

reaction of iodide **5**.[19] Alternatively, the RCM reaction can be used as the first key step to form the C5−C6 double bond of either the 12-membered ring to obtain iodide **6** (path B) or the 8-membered ring of compound **8** (path C), in which Y can denote an halomethylidene group or its synthetic precursor. The second key step would be the intramolecular Heck cyclization of the corresponding iodides to construct the ring A. A key factor in the formation of the AB system by strategy B would be the preference of Heck reactions for 6-*exo* cyclization.[9,20] We envisaged that in both cases the initial RCM would involve the less-substituted double bonds, starting the process at the monosubstituted double bond and producing the appropriate precursor for the final Heck cyclization.

Our first target for both paths A and B was iodide **5**, which was prepared from 4-pentyn-1-ol (Scheme 1). Swern oxidation followed by addition of allylmagnesium bromide afforded alcohol **11a** in 70% yield (two steps), and metalation of its silyl ether **11b** with butyllithium, followed by reaction of the resulting lithium derivate with *p*-formaldehyde, afforded propargyl alcohol **12**, successive treatment of which with sodium bis(2-methoxyethoxy)-aluminum hydride and freshly sublimed iodine produced the Z-vinyl iodide **5**.

For the synthesis of **1** it is the 4*S* enantiomer of **11a** that is of interest. Although it can be prepared enantioselectively in 66% yield by treating 4-pentynal with an equimolecular amount of an allylborane prepared from (−)-*β*-methoxydiisopinylcampheylborane,[21] we evaluated a catalytic strategy. Treatment of 4-pentynal under Carreira conditions, with a 150 mol % excess of allyltrimethylsilane in the presence of 10 mol % of (*R*)-BINOL and TiF_4,[22] gave alcohol (4*S*)-1-octen-7-yn-4-ol [(4*S*)-**11a**] in only 62% yield and 70% ee.[23] However, higher yield (81%) and an enantiomeric excess of 97% were obtained when the reaction was carried out at 0 °C with allyltributylstannane and 10 mol % of catalyst prepared by heating a 2:1 mixture of (*R*)-BINOL and Ti(O-*i*-Pr)$_4$.[24]

In pursuance of path A, compound **4** was prepared as the only detectable product of the Heck cyclization of iodide **5** with $(Ph_3P)_4Pd/Et_3N$ in refluxing acetonitrile.[25] Although alcohol **4** was obtained in good yield, we decided to explore the feasibility of the RCM reaction using a substrate prepared from the more readily available alcohol **14a** instead of bromide **13**.[26] Thus, treatment of alcohol **14a** with triphenylphosphine and carbon tetrabromide in dichloromethane provided bromide **14b** in 81% yield; reaction of the freshly prepared bromide with

(19) Preliminary studies had shown the viability of the Heck cyclization of iododiene **5**, see: Codesido, E. M.; Cid, M. M.; Castedo, L.; Mouriño, A.; Granja, J. R. *Tetrahedron Lett.* **2000**, *41*, 5861−5864.

(20) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E.-i. *J. Am. Chem. Soc.* **1992**, *114*, 10091−10092.

(21) White, J. D.; Kim, T.-S.; Nambu, M. *J. Am. Chem. Soc.* **1997**, *119*, 103−111. Alcohol (4*R*)-**11a** was obtained in 95% ee; $[\alpha]^{25}_D$ +35.4 (*c* 2.36, $CHCl_3$).

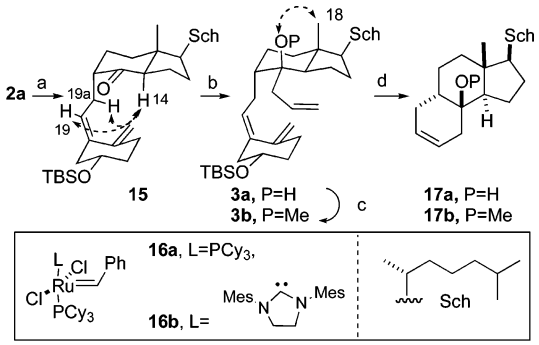
(22) Gauthier, D. R., Jr.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2363−2365.

(23) The absolute configuration of (4*S*)-**11a** was inferred from the effects of the phenyl groups of its *R* and *S* methoxyphenylacetic esters on the chemical shifts of the C3 and C5 protons. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370−2374.

(24) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467−8468

(25) Mascareñas, J. L.; García, A. M.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1992**, *33*, 4365−4368.

SCHEME 2. Preparation and RCM Products of Trienes 3a and 3b[a]

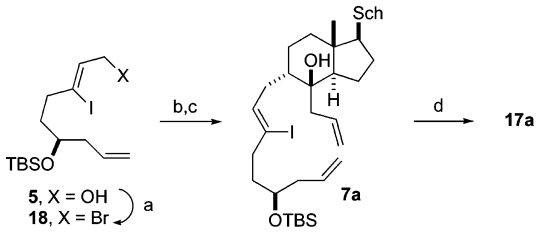


[a] Reagents and conditions: (a) (i) LDA, THF, −78 °C, (ii) **14b**, 85%; (b) allylMgBr, THF, 91%; (c) HK, MeI, 18-crown-6, THF, 85%; (d) **16b**, CH_2Cl_2, Δ, 90% (**17a**), 87% (**17b**).

the kinetic enolate of Grundmann's ketone (**2a**),[27] formed by LDA treatment of **2a** at −78 °C, afforded ketone **15** in high yield (Scheme 2), and treatment of **15** with 4 equiv of allylmagnesium bromide gave the desired RCM substrate, alcohol **3a**, in almost quantitative yield. The relative stereochemistry of the newly generated stereocenters was confirmed by inspection of the two-dimensional NMR spectra of **15** and **3b**: the clear NOE relationship between H14 (δ 2.40 ppm) and both H19 (δ 5.04 ppm) and the neighboring allyl protons H19a (δ 1.81 ppm) in compound **15** showed the axial orientation of pentadienyl moiety, while the significant interaction between Me18 and the methoxy group in the NOESY spectrum of **3b** showed their *cis* relationship. Compound **3b** was prepared by heating a THF solution of **3a** in the presence of KH, 18-crown-6, and MeI, because only very low yields were obtained with NaH as base, even after long reaction times in the presence of 15-crown-5. Also, even under typical conditions for hindered alcohols, all attempts to introduce different protecting groups, such as tertbutydimethylsilyl, benzyl, acetate, or tosylate, were unsuccessful, showing the inaccessibility of this hydroxy group.

Unfortunately, when **3a** was subjected to RCM conditions using 15% Grubbs' catalyst (**16a**)[28] in refluxing methylene chloride or benzene, no reaction took place, only unaltered starting material was recovered; only after long reaction times in refluxing benzene was a dimeric byproduct resulting from a cross-metathesis reaction of the least substituted double bond obtained. Reaction of **3b** also failed, showing that it was not the homoallylic hydroxy group that was responsible for the lack of reactivity. When the more reactive ruthenium catalyst **16b** was used, both **3a** and **3b** reacted, but the products containing the steroidal CD fragment (obtained in high yield) were **17a** and **17b**, i.e., formation of the six-membered ring had prevailed over formation of the eight-membered ring even though it involved reaction with the more substituted olefin. This result was not completely

SCHEME 3. Preparation of Triene 7a and Evaluation of Its RCM Reaction[a]



[a] Reagents and conditions: (a) CBr_4, Ph_3P, CH_2Cl_2, 98%; (b) LDA, **2a**, THF, −78 °C, 55%; (c) AllylMgBr, THF, 85%; (d) **16a**/**16b**, CH_2Cl_2, Δ, 70−85%.

unexpected, given that 1,2-*cis* disubstituted cyclohexanes such as **3** are known to undergo RCM to [6.4.0] systems less readily than the corresponding *trans* systems.[29,7a] Apparently, **3** did not possess those features (a conformationally predisposed diene or an adequately oriented polar functional group) that have allowed previous RCM constructions of cyclooctene.[8]

In view of the above results, we turned to the other strategy starting from **5**, path B (Figure 2), in which the formation of a 12-membered ring by RCM of triene **7** would precede 6-*exo* intramolecular Heck cyclization. Compound **7a** was straightforwardly obtained by alkylation of the LDA-formed kinetic enolate of **2a** with bromide **18** (prepared by treatment of alcohol **5** with carbon tetrabromide and triphenylphosphine), followed by allylation of the resulting ketone,[30] but when **7a** was subjected to RCM conditions using Grubbs' catalyst (**16a**) or **16b**, compound **17a** was obtained instead of the desired iodide **6**. Once more, formation of the six-membered ring had prevailed over macrocyclization, even though it involved reaction with the more substituted olefin (Scheme 3).[13b]

In view of the discouraging behavior of **3** and **7**, we decided to check whether the formation of cyclooctene on **2a** or **2b**[31] by RCM was feasible in the absence of the competing double bonds featured by the substrates of paths A−C. An additional issue of interest was how the presence of the ring A precursor or other substituents would affect the course of the RCM reaction. We therefore aimed to prepare compounds **21a**−**i** from compounds **20** (Scheme 4), for which the otherwise competing and preferred cyclohexene pathway was now not possible because they have no internal double bond. However, preparation of compounds **20** by alkylation of the enolate of **2a/b** was more troublesome than preparation of **15** or its path B counterpart because of the lower reactivity of the alkyl halides required for compounds **20**. Thus, addition of 1-iodopent-4-ene or 5-iodo-2-methylpent-1-ene

(26) Toh, H. T.; Okamura, W. H. *J. Org. Chem.* **1983**, *48*, 1414−1417.

(27) Ketone **2a** is readily obtained by ozonolysis of vitamin D_3, see: Mascareñas, J. L.; Sarandeses, L.; Castedo, L.; Mouriño, A. *Tetrahedron* **1991**, *47*, 3485−3498.

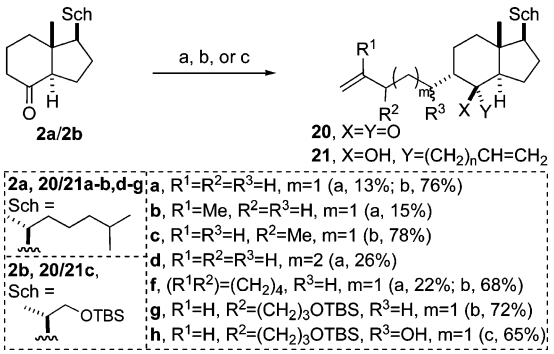
(28) The amount of Grubbs' catalyst has not been optimized and 15% has been routinely used in this work.

(29) (a) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108−2109. (b) For an example of tricyclic system formation using a *cis*-diene, see: Holt, D. J.; Barker, W. D.; Jenkins, P. R.; Davies, P. R.; Garrat, S.; Fawcet, J.; Russell, D. R.; Ghosh, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3298−3300. (c) 1,2-Cis disubstituted cyclopentane derivatives are also worse substrates than the trans dienes: Paquete, L. A.; Mendez-Andino, J. *Tetrahedron Lett.* **1999**, *40*, 4301−4304. (d) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746−9749.

(30) The relative stereochemistries of both enolate alkylation and ketone allylation were determined by NOE.

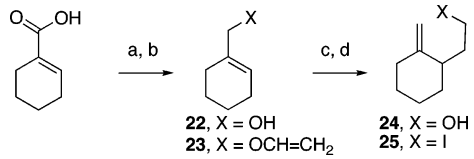
(31) (a) Leyes, G. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6099−6105. (b) Sardina, F. J.; Mouriño, A.; Castedo, L. *J. Org. Chem.* **1986**, *51*, 1264−1269.

SCHEME 4. α-Alkylations of Ketones 2a or 2b[a]



[a] Reagents and conditions: (a) LDA, $CH_2{=}CR^1CHR^2(CH_2)_mCH_2I$, THF, −78 °C; (b) KHMDS, $CH_2{=}CR^1CHR^2(CH_2)_mCH_2I$, DMF/toluene (1:1), −78 °C; (c) LDA,$CH_2{=}CHCH[(CH_2)_3OTBS]CH_2CHO$, THF, −78 °C.

SCHEME 5. Preparation of 2-Methylene-1-(2-iodoethyl)cyclohexane[a]



[a] Reagents and conditions: (a) $LiAlH_4$, Et_2O, 90%; (b) $CH_2{=}CHOBu$, $Hg(OAc)_2$, 160 °C; (c) $NaBH_4$, MeOH, 82% (two steps); (d) I_2, Ph_3P, Im, 67%.

to the LDA-generated enolate of **2a** under the conditions used in the earlier alkylations gave **20a** and **20b** in yields of only 13% and 15%, respectively (Scheme 4). In experiments seeking to improve the yield of the 1-iodopent-4-ene reaction, no significant advantage was achieved by using lithium hexamethyldisilazide (LiHMDS) as base, or by changing the leaving group to the more reactive triflate, or by adding chelating agents such as HMPA or TMEDA, or by using Na or K as the counterion of the base (even when 15-crown-5 ether was added to complex the Na ion, in which case a large amount of epimerized ketone was detected). Only the use of Palomo conditions (1:1 DMF/toluene as solvent, KHMDS as base)[32] provided a high yield of **20a** (76%). Yields of 65−78% were also achieved with other alkylating agents (Scheme 4), the lowest corresponding to the most hindered, 2-methylene-1-(2-iodoethyl)cyclohexane (**25**), the precursor of ketone **20f**. This iodide, a monoene analogue of **4**, was prepared from 1-cyclohexenecarboxylic acid by reduction with lithium aluminum hydride and condensation of the resulting alcohol (**22**) with butyl vinyl ether in the presence of $Hg(OAc)_2$ to obtain the corresponding vinyl ether **23** (80% yield). Claisen rearrangement of **23** by heating it in silane in a sealed tube, in situ reduction of the rearrangement product with sodium borohydride gave alcohol **24** (yield, 69%); **24** can also be obtained from **22** in one step and 82% yield by heating a solution of this alcohol in butyl vinyl ether at 160 °C followed by in situ reduction (Scheme 5). Final treatment of **24** with triphenylphosphine, imidazole, and iodine gave the corresponding iodide in overall yield (49%) for the four steps.

(32) Palomo, C.; Oiarbide, M.; Mielgo, A.; González, A.; García, J.; Landa, C.; Lecumberri, A.; Linden, A. *Org. Lett.* **2001**, *3*, 3249−3252.

Addition of 4 equiv of allymagnesium bromide to ketones **20a**−**g** and of 4 equiv of vinylmagnesium bromide to **20d** gave the required dienes **21a**−**g** in good yields. The results of subjecting them to RCM conditions are listed in Table 1. With the appropriate catalyst (**16b** in the case of the gem-disubstituted olefins **21b** and $\mathbf{21b}^{Me}$), substrates **21a**, **21b**, $\mathbf{21b}^{Me}$, **21c**, and **21g** afforded the desired eight-membered rings in yields of 86−99% (entries 1, 3, 5, 6, and 12), although **21g** needed a week in refluxing solvent (methylene chloride or benzene) regardless of whether the catalyst was **16a** or **16b**. Compound **21i**,[33] a ketone derivative of **21g**, also cyclized in very high yield (although like **21g** it needed long reaction times), suggesting that a small modification of substrate geometry does not significantly affect the reaction (entry 14), while a diasteromic mixture of diols **21h** did not cyclize (entry 13).[34] Moreover, elongation of the longer alkenyl chain by one carbon ($m = 2$, entry 7) allowed the formation of a nine-membered ring, also in good yield, showing that these systems are well preorganized for the formation of medium-size rings by RCM. However, entries 8 and 9 show that cyclization does not take place unless there is at least one methylene group between the oxygenated carbon and the double bond of the olefin chain it bears, since **21e** and $\mathbf{21e}^{Me}$ failed to cyclize regardless of changes of solvent, catalyst, and alcohol-protecting group. The cyclohexyl derivative **21f** [$R^1R^2 = (CH_2)_4$, entry 10] also completely failed to cyclize, lengthy heating in refluxing benzene only bringing about metathetic dimerization. These results show that the constrains introduced by the cyclohexane ring, more than olefin substitution, play the most important role in the formation of cyclooctene in this system.

The reactions of **21c**, **21g**, and **21i**, in which the products were obtained in yields of 95−99% as approximately 1:1 mixtures of diastereomers, show that formation of the eight-membered ring is not impeded by a substituent R^2 at C10, whatever its stereochemistry at this position.[35] That the reactions of **21g** and **21i** were so much slower than that of **21c** (or **21a** and **21b**) may perhaps be due to coordination of their OTBS oxygens to the ruthenium catalyst (**27g-II**),[36] which would delay the olefin coordination (**27g-I**) that is necessary for ring formation (Figure 3);[37] and such coordination may also

(33) Compound **21h** was prepared by addition of aldehyde **31** (Scheme 6) to the LDA-generated enolate of **2a** in THF, followed by treatment of the resulting ketone with allylmagnesium bromide and oxidation with PDC.

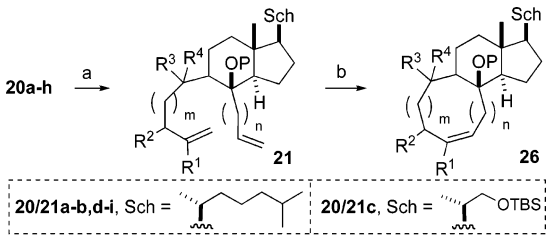
(34) The presence of two nucleophilic hydroxy goups has been proposed to decompose the catalyst, see: Hyldtoft, L.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 8444−8452 and also ref 7d.

(35) The (10*S*)-**26g**/(10*R*)-**26g** ratio was almost 1:1 after 48 and after 76 h. For an example of stereocontrolled RCM, see: Huwe, C. M.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2376−2378.

(36) (a) Heteroatom coordination has been reported to participate in and help the formation of medium sized rings, Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130−9136. (b) Heteroatom coordination has also been thought to be responsible for the remarkable stability of certain ruthenium carbene complexes that have been isolated: Kingsbury, J. S.; Harrity, J. P. A.; Bonittatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791−799. (c) A similar ligation has been exploited in a robust and reusable polymer-bound ruthenium carbene catalyst: Yao, Q. *Angew. Chem., Int. Ed.* **2000**, *39*, 3896−3898.

(37) For recent studies of metathesis mechanisms, see: Adlhart, C.; Chen, P. *J. Am. Chem. Soc.* **2004**, *126*, 3496−3510. Cavallo, L. *J. Am. Chem. Soc.* **2002**, *124*, 8965−8973.

TABLE 1. Results of RCM of Dienes 21a–i



entry	substrate	P	R^1	R^2	R^3	R^4	*m*	*n*	catalyst	yield, %[a]
1	**21a**	H	H	H	H	H	1	1	**16a**	86
2	**21b**	H	Me	H	H	H	1	1	**16a**	nd[b]
3	**21b**	H	Me	H	H	H	1	1	**16b**	86
4	**21b**^{Me}	Me	Me	H	H	H	1	1	**16a**	nd
5	**21b**^{Me}	Me	MeH	H	H	H	1	1	**16b**	89
6	**21c**	H	H	Me	H	H	1	1	**16a**	99[c]
7	**21d**	H	H	H	H	H	2	1	**16a**	63
8	**21e**	H	H	H	H	H	2	0	**16a/16b**	nd
9	**21e**^{Me}	Me	H	H	H	H	2	0	**16a/16b**	nd
10	**21f**	H		$(CH_2)_4$	H	H	1	1	**16a/16b**	nd
11	**21f**^{Me}	Me		$(CH_2)_4$	H	H	1	1	**16a/16b**	nd
12	**21g**	H	H	$(CH_2)_3$OTBS	H	H	1	1	**16a**	95[c]
13	**21h**	H	H	$(CH_2)_3$OTBS	OH/H		1	1	**16a/16b**	nd
14	**21i**	H	H	$(CH_2)_3$OTBS	=O		1	1	**16a**	97[c]

[a] Isolated yields of **26**. [b] nd, not detected in reaction crude by ^{1}H NMR (a variety of solvents were used). [c] **26c**, **26g**, and **26i** were obtained as inseparable mixtures of C10 epimers.

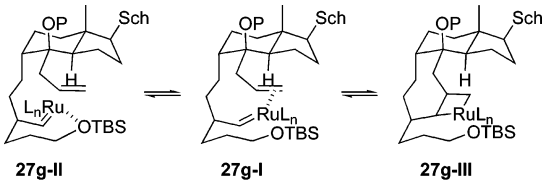


FIGURE 3. Possible cause of the longer reaction time of dienes **21g** and **21h**.

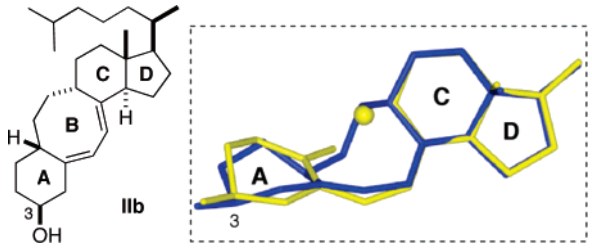


FIGURE 4. Structure of transition state analogue **IIb** and superimposition of its ring system (blue) on that of the putative transition state structure of the preD$_3$-D$_3$ isomerization reaction ([1,7]-H Ts, yellow).

explain why the Ru methylidene catalyst survived for so much longer than its normal half-life, 40 min. [38]

To sum up, all these results showed that formation of the eight-membered ring by RCM was possible. Although they also suggested that the constrains introduced by the cyclohexane rings of **21f** and **3** prevented adoption of the conformation required for the annulation, they left open the possibility of successful approach to compounds **1** by path C.

In evaluating path C, we focused on the preparation of **IIb**, the conformity of which with [1,7]-H Ts is illustrated in Figure 4. To avoid competition from the =Y olefin of **9** during RCM, RCM would be applied to diene **21g**, after which the OTBS group of the product, **26g**, would be replaced by the vinyliodide moiety required for formation of ring A by Heck cyclization.

Diene **21g** was prepared as sketched above, by alkylation of the enolate of **2a** under Palomo conditions followed by allylation. The required alkylating agent, iodide **30**, was prepared from 4-pentyn-1-ol:[13b] protection with TBSCl, metalation with *n*-BuLi and entrapment of the resulting anion with *p*-formaldehyde, and semihydrogenation afforded compound **28** in 63% overall yield; condensation of **28** with butyl vinyl ether in the presence of Hg(OAc)$_2$, followed by Claisen rearrangement and in situ reduction with sodium borohydride, then provided alcohol **29** in 69% yield from **28**; and exposure of this alcohol to triphenylphosphine, imidazole, and iodine gave the desired iodide **30** (Scheme 6).[39] Diene **21g** was obtained as an inseparable 1:1 mixture of C10-epimers as was **26g** (obtained as described above by a one-week RCM reaction in refluxing CH_2Cl_2). However, after removal of the TBS group with TBAF, the resulting alcohols, **32a** and **32b** (Scheme 7), were easily separated, although it was not possible to establish their C10-stereochemistries at this stage by NMR experiments.

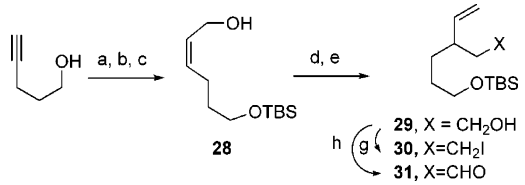
Oxidation of isomer **32a** with PDC and subsequent olefination by Stork's method[40] produced the (*Z*)-vinyl iodide **34a** in 72% yield (Scheme 7), and a 2-h Heck reaction with palladium tetrakistriphenylphosphine in

(38) (a) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202–7207. (b) Sanford, M. S.; Love, J. A. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 1, pp 112–131. (c) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415.

(39) PDC oxidation of alcohol **29** gave aldehyde **31**, which was used in the preparation of diene **21h**.

(40) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173–2174.

SCHEME 6. Synthesis of Iodide 30 and Aldehyde 31[a]



[a] Reagents and conditions: (a) TBSCl, Im, CH_2Cl_2, 92%; (b) *n*-BuLi, THF, $(H_2CO)_n$, 82%; (c) H_2, Lindlar, hexanes, 83%; (d) CH_2=CHOBu, $Hg(OAc)_2$, 160 °C; (e) $NaBH_4$, MeOH, 69% (from **28**); (g) I_2, Ph_3P, Im, 76%; (h) PDC, CH_2Cl_2, 69%.

refluxing acetonitrile yielded compound **36a** as a single isomer. Disappointingly, the yield of **36a** was only 15%, the major product being the protonated compound **35** (>40% yield). The use of other catalyst systems, such us $Pd(OAc)_2/PPh_3/Et_3N$ in DMF or acetonitrile, did not achieve any improvement. By contrast, applying the same reaction sequence to **32b** gave a 64% yield of the *trans*-bicyclo compound **36b** as the only product. These differences in reactivity of iodides **34a** and **34b** must be due to conformational restrictions introduced by the eight-membered ring fused to the CD-bicyclic system. The *trans* relative stereochemistry of **36a** at C5 and C10 was established on the basis of the coupling of the C5 proton to those on C6 and C10, C5−H appearing as a triplet[41] with a *J* value, 9.3 Hz, that in cyclohexanes is characteristic of the *trans* axial−axial orientation. The *R* configuration of C10 was then established when a substantial NOESY cross-peak between H14 and H5 showed them to be *cis* to each other.[13] The 10*S* stereochemistry of **36b** was similarly shown by an H5−H10 coupling constant of 9.3 Hz and a NOE enhancement between H5 and H9 suggestive of a *cis* relationship.

Conclusion

In conclusion, we have shown that RCM is a suitable method for formation of the eight-membered carbocycle of the novel steroid-like framework of compounds **1** and that it can be followed by Heck cyclization to build tricyclo[10.4.0.0^{4,9}]hexadecane systems. Notably, the complete reaction sequence (enol alkylation,[42] ketone allylation,[43] RCM, and Heck cyclization) is stereoselective. In particular, whether the final product is a *cis-cisoid-trans* or a *cis-transoid-trans* system is determined by the stereochemistry of the alkylating agent, which in our case ultimately derives from a Claisen rearrangement.[44] It is envisaged that this approach will allow access to general fused 6-8-*n* systems starting from *n*-membered cycloalkanones.

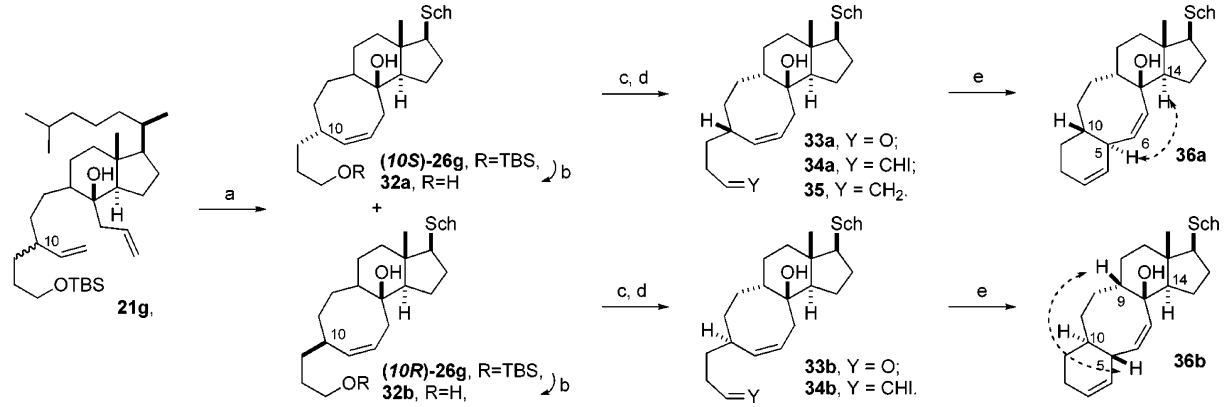
Experimental Section

Preparation of Ketone 15. Carbon tetrabromide (232 mg, 0.70 mmol) was added to a solution of alcohol **14a**[26] (150 mg, 0.56 mmol) in CH_2Cl_2 (6 mL). The resulting solution was cooled to 0 °C and Ph_3P (220 mg, 0.84 mmol) was added. The reaction mixture was stirred for 30 min at room temperature and the solvent was removed under reduced pressure, giving a residue that when flash chromatographed (1% EtOAc/hexanes) afforded 150 mg of bromide **14b** and used without further characterization [81%, R_f 0.8 (10% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.54 (1H, t, J = 8.3 Hz), 5.02 (1H, s), 4.93 (1H, s), 4.11 (2H, d, J = 8.2 Hz), 3.85 (1H, m), 0.87 (9H, s), 0.05−0.04 (6H, 2s).

A solution of ketone **2a**[27] (100 mg, 0.38 mmol) in THF (4 mL) was added under Ar to a freshly prepared solution of LDA in THF (1 M, 760 μL, 0.76 mmol) at −78 °C. The reaction mixture was stirred at that temperature for 30 min and then a solution of **14b** (251 mg, 0.75 mmol) in THF (6 mL) was added. The resulting solution was stirred at −78 °C for 3 h, and the reaction was quenched by adding H_2O (5 mL). The aqueous layer was extracted with Et_2O and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure, giving a residue that upon flash chromatography (2% EtOAc/hexanes) afforded 165 mg of ketone **15** [85%, R_f 0.6 (10% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.04 (1H, t, J = 7.2 Hz), 4.94 (1H, s), 4.63 (1H, s), 3.78 (1H, tt, J = 7.2 and 3.6 Hz), 2.46 (1H, dd, J = 11.5 and 7.4 Hz), 2.30 (4H, m), 2.22 (1H, m), 2.09 (1H, dd, J = 12.9 and 7.5 Hz), 0.91 (3H, d, J = 6.2 Hz), 0.85 (9H, s), 0.84 (6H, overlapped d, J = 6.6 Hz), 0.61 (3H, s), 0.03 (6H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.9, 145.9, 139.0, 122.9, 110.7, 69.9, 58.2, 56.8, 50.3, 49.8, 46.4, 39.4, 36.1, 35.9, 35.5, 35.4, 32.4, 31.1, 28.0, 27.7, 27.6, 25.8, 23.8, 22.8, 22.5, 19.0, 18.6, 18.1, 12.9, −4.7, −4.8. IR ν_{mas} (KBr, cm^{-1}) 2954, 2858, 1712, 1469, 1381, 1253, 1093, 1009, 898, 836, 774. MS *m/z* 515 (MH^+, 41), 499 ($M^+ - CH_3$, 35), 457 ($M^+ - {}^t$Bu, 100), 383 (83), 365 (62). HRMS calcd for $C_{33}H_{59}O_2Si$ (MH^+) 515.4284, found 515.4276.

Preparation of Ketone 20a (KHMDS Method). A solution of ketone **2a** (313 mg, 1.18 mmol) in DMF (3.0 mL) was

SCHEME 7. Preparation of Vinyl Iodides 34a and 34b (path C) and Cyclization To Provide the Wished Tetracyclic System by Heck Reaction[a]



[a] Reagents and conditions: (a) **16a**, CH_2Cl_2, 6 days, 95%; (b) TBAF, THF, 87%; (c) PDC, CH_2Cl_2, 57% for **33a**, 66% for **33b**; (d) $Ph_3P^+CH_2I$ I^-, NaHMDS, THF, 72% for **34a**, 70% for **34b**; (e) $Pd(PPh_3)_4$, CH_3CN, Δ, 15% for **36a**, 64% for **36b**.

added under Ar to a solution of KHMDS in toluene (0.5 M, 4.70 mL, 2.35 mmol) and DMF (3 mL). The reaction mixture was stirred for 30 min and then 1-iodopent-4-ene (464 mg, 2.36 mmol) was added. The reaction mixture was stirred for 2 h at −78 °C, and the reaction was quenched by addition of a solution of NH_4Cl (4 mL). The aqueous layer was extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure, giving a residue that when flash chromatographed (3% EtOAc/hexanes) afforded 210 mg of ketone **20a** [76%, R_f 0.6 (10% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.74 (1H, ddt, J = 17.0, 10.3, and 6.7 Hz), 4.95 (1H, dq, J = 17.0 and 1.7 Hz), 4.92 (1H, ddt, J = 10.3, 1.9, and 0.9 Hz), 2.57 (1H, dd, J = 11.6 and 7.4 Hz), 2.26 (1H, q, J = 7.5 Hz), 0.92 (3H, d, J = 6.4 Hz), 0.85 and 0.84 (6H, overlapped d, J = 6.6 Hz), 0.62 (3H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 215.2, 138.3, 114.7, 57.9, 56.8, 50.0, 49.7, 39.4, 35.9, 35.5, 35.5, 33.4, 33.2, 28.6, 28.0, 27.5, 26.8, 23.7, 22.7, 22.5, 18.9, 18.6, 12.8. IR ν_{mas} ($CHCl_3$, cm^{-1}) 3068, 2948, 2952, 2864, 2247, 1708, 1640, 1459, 1383, 1238, 991. MS *m/z* 333 (MH^+, 100), 315 ($MH^+ - H_2O$, 54), 264 (30), 221 (28). HRMS calcd for $C_{23}H_{41}O$ (MH^+) 333.3157, found 333.3157. Elemental Anal. Calcd: C 83.06; H 12.13. Found: C 83.32; H 12.02.

Ketone 20b (LDA Method). A solution of ketone **2a** (330 mg, 1.25 mmol) in THF (12 mL) was added under Ar to a freshly prepared solution of LDA in THF (1 M, 2.5 mL, 2.5 mmol) at −78 °C. The reaction mixture was stirred at that temperature for 30 min and then a solution of 5-iodo-2-methylpent-1-ene (520 mg, 2.5 mmol) in THF (18 mL) was added. The resulting solution was stirred at −78 °C for 3 h, and the reaction was quenched by adding H_2O (10 mL). The aqueous layer was extracted with Et_2O and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure, giving a residue that upon flash chromatography (2% EtOAc/hexanes) afforded 65 mg of ketone **20b**[31] [15%, R_f 0.6 (10% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.68 (1H, s), 4.63 (1H, s), 2.57 (1H, dd, J = 11.8 and 7.4 Hz), 2.27 (1H, q, J = 6.6 Hz), 0.92 (3H, d, J = 6.4 Hz), 0.85 and 0.84 (6H, overlapped d, J = 6.6 Hz), 0.62 (3H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 215.2, 145.3, 110.1, 57.9, 56.7, 50.0, 49.8, 39.4, 37.4, 35.9, 35.5, 35.5, 32.3, 28.6, 28.0, 27.5, 25.4, 23.7, 22.7, 22.5, 18.9, 18.6, 12.8. IR ν_{mas} (KBr, cm^{-1}) 2954, 2869, 1711, 1465, 1380, 886. MS *m/z* 347 (MH^+, 72), 329 ($MH^+ - H_2O$, 31), 279 (100). HRMS calcd for $C_{24}H_{43}O$ (MH^+) 347.3313, found 347.3306. Elemental Anal. Calcd: C 83.16; H 12.22. Found: C 83.01; H 12.06.

Ketone 20g. To a solution of alcohol **29** (0.50 g, 1.90 mmol) in THF (10 mL) at 0 °C and under Ar were successively added Ph_3P (610 mg, 2.32 mmol), imidazole (396 mg, 5.80 mmol), and I_2 (541 mg, 2.13 mmol). The resulting mixture was stirred at room temperature for 30 min and then H_2O (8 mL) was added. The aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure, giving a residue that upon flash chromatography (hexanes) afforded 0.5 g of iodide **30** and used without further characterization [76%, R_f 0.85 (10% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.43 (1H, m), 5.06 (2H, m), 3.58 (2H, t, J = 6.3 Hz), 3.22 (1H, ddd, J = 9.5, 8.0, and 5.5 Hz), 3.02 (1H, dt, J = 9.5 and 8.0 Hz), 0.88 (9H, s), 0.03 (6H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.9, 116.1, 63.0, 44.6, 38.5, 30.7, 30.2, 26.0, 18.3, 5.0, −5.3.

Using the conditions described for the preparation of **20a**, 233 mg of ketone **20g** was obtained from ketone **2a** and iodide **30** [72%, R_f 0.5 (10% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.44 (1H, m), 4.92 (1H, dt, J = 8.5 and 1.0 Hz), 4.90 (1H, dd, J = 7.3 and 1.9 Hz), 3.54 (2H, t, J = 6.2 Hz), 2.51 (1H, m), 0.91 (3H, d, J = 6.1 Hz), 0.86 (9H, s), 0.85 (6H, d, J = 6.6 Hz), 0.60 (3H, s), 0.008 (6H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 215, 142.6, 114.8, 63.1, 57.9, 56.7, 50.1, 50.0, 43.9, 39.4, 35.9, 35.4, 33.0, 31.0, 30.5, 30.3, 28.8, 28.5, 28.0, 27.5, 25.9, 23.7, 22.7, 22.5, 18.9, 18.7, 18.3, 12.7, −5.3. IR ν_{mas} ($CHCl_3$, cm^{-1}) 3072, 2957, 2929, 2855, 1710, 1634, 1469, 1384, 1363, 1254. MS *m/z* 505 (MH^+, 100), 489 (46), 447 (92), 373 (33). HRMS calcd for $C_{32}H_{61}O_2Si$ (MH^+) 505.4441, found 505.4416.

General Method for Ketone Allylation: Preparation of Alcohol 3a. A solution of ketone **15** (77 mg, 0.15 mmol) in THF (2 mL) was added under Ar to a solution of allylmagnesium bromide (1 M in THF, 450 μL, 0.45 mmol) in THF (1.5 mL) at −78 °C. The reaction mixture was stirred at that temperature for 3 h and NH_4Cl (sat. dil., 4 mL) was added. The aqueous layer was extracted with Et_2O and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure, giving a residue that when flash chromatographed (2% EtOAc/hexanes) afforded 76 mg of compound **3a** [91%, R_f 0.6 (10% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.84 (1H, dddd, J = 16.8, 10.3, 8.3, and 6.5 Hz), 5.15 (1H, dd, J = 10.1 and 2.2 Hz), 5.12 (1H, dd, J = 17.1 and 1.9 Hz), 5.08 (1H, t, J = 7.0 Hz), 4.94 (1H, dt, J = 2.6 and 1.3 Hz), 4.65 (1H, d, J = 2.7 Hz), 3.90 (1H, tt, J = 6.6 and 3.3 Hz), 0.92 (3H, s), 0.86 (9H, s), 0.85 and 0.84 (6H, overlapped d, J = 6.6 Hz), 0.04−0.03 (6H, 2s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.6, 137.4, 133.4, 125.4, 119.2, 110.3, 75.8, 69.5, 57.3, 51.5, 46.3, 43.5, 43.3, 39.5, 36.0, 35.9, 35.3, 34.8, 32.0, 28.0, 27.2, 27.1, 25.8, 23.9, 22.8, 22.5, 21.0, 20.0, 18.3, 18.1, 13.4, −4.7, −4.8. IR ν_{mas} ($CHCl_3$, cm^{-1}) 3667, 3599, 3568, 3078, 2952, 2860, 1724, 1635, 1469, 1366, 1253, 1199, 1086, 1007. MS *m/z* 539 ($M^+ - H_2O$, 77), 515 (27), 499 (42), 407 (100). HRMS calcd for $C_{36}H_{63}OSi$ ($M^+ - H_2O$) 539.4648, found 539.4639.

Alcohol 21a. Using the conditions described for the preparation of **3a**, 53 mg of alcohol **21a** was obtained from **20a** [94%, R_f 0.6 (10% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.82 (2H, m), 5.15 (1H, dd, J = 10.2 and 2.2 Hz), 5.11 (1H, ddt, J = 17.0, 2.2, and 1.1 Hz), 5.00 (1H, ddd, J = 17.0, 3.5, and 1.6 Hz), 4.93 (1H, ddt, J = 10.2, 1.9, and 1.0 Hz), 2.25, (1H, dd, J = 14.2 and 6.6 Hz), 2.11 (1H, dd, J = 14.2 and 8.2 Hz), 0.93 (3H, s), 0.88 (3H, d, J = 6.8 Hz), 0.86 and 0.85 (6H, overlapped d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.9, 133.3, 119.2, 114.4, 76.0, 57.1, 51.5, 43.5, 43.4, 42.5, 39.5, 39.4, 35.9, 35.2, 34.8, 34.0, 28.0, 27.5, 27.2, 23.7, 22.8, 22.5, 20.3, 20.0, 18.4, 13.4. IR ν_{mas} ($CHCl_3$, cm^{-1}) 3667, 3076, 2950, 2872, 1639, 1466, 1382, 994, 910. MS *m/z* 375 (MH^+, 38), 357 ($MH^+ - H_2O$, 64), 333 (100), 315 (80). HRMS calcd for $C_{26}H_{47}O$ (MH^+) 375.3627, found 375.3613.

Alcohol 21g. Using the conditions described for the preparation of **3a**, 720 mg of alcohol **21g** were obtained from **20g** [82%, R_f 0.5 (10% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.80 (1H, m), 5.51 (1H, m), 5.16−4.90 (4H, m), 3.57 (2H, t, J = 6.3 Hz), 2.21 (1H, dd, J = 13.9 and 6.5 Hz), 2.08 (1H, dd, J = 13.9 and 8.2 Hz), 0.93 (3H, s), 0.88 (9H, s), 0.85 and 0.84 (6H, overlapped d, J = 6.6 Hz), 0.03 (6H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.1, 133.4, 119.2, 114.5, 76.1, 63.3, 57.0, 51.6, 51.6, 43.8, 43.4, 42.6, 39.5, 35.9, 35.3, 34.8, 33.6, 31.2, 30.4, 28.0, 27.2, 26.0, 25.1, 23.8, 22.8, 22.5, 20.3, 20.0, 18.4, 18.3, 13.4, −5.3. MS *m/z* 529 ($MH^+ - H_2O$, 49), 505

(41) H4−H5 coupling was close to zero.

(42) For some examples of stereoselective enol alkylation, see: (a) Hughes, D. L. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Chapter 34.1. For a review of asymmetric protonation of enolates, see: (b) Yanagisawa, A.; Yamamoto, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Chapter 34.2.

(43) For a recent study of the diastereoselectivity of cycloalkanone alkylation, see: (a) Gung, B. W. *Chem. Rev.* **1999**, *99*, 1377−1386. (b) Ohwada, T. *Chem. Rev*. **1999**, *99*, 1337−1376.

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(100), 487 (28), 471 (30), 397 (48). HRMS calcd for $C_{35}H_{65}OSi$ ($MH^+ - H_2O$) 529.4805, found 529.4806.

Compound 3b. A solution of alcohol **3a** (38 mg, 0.07 mmol) in THF (0.5 mL) was treated under Ar with KH (6 mg, 0.15 mmol) and MeI (9 μL, 0.15 mmol). After the resulting solution was stirred for 8 h, the reaction was quenched by addition of H_2O and the resulting mixture was extracted with hexanes. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure, giving a residue that when flash chromatographed (hexanes) afforded 33 mg of compound **3b** [85%, R_f 0.75 (10% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.90 (1H, m), 5.12−5.03 (3H, m), 4.94 (1H, d, J = 2.8 Hz), 4.65 (1H, d, J = 2.4 Hz), 3.90 (1H, tt, J = 6.2 and 3.1 Hz), 3.21 (3H, s), 0.91 (3H, s), 0.87 (9H, s), 0.85 and 0.84 (6H, overlapped d, J = 6.6 Hz), 0.04−0.03 (6H, 2s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.7, 137.2, 135.1, 125.7, 116.3, 110.2, 75.9, 69.4, 57.1, 52.5, 49.6, 46.3, 43.5, 40.2, 39.5, 39.1, 35.9, 35.3, 34.9, 32.0, 28.0, 27.4, 26.8, 25.8, 23.9, 22.8, 22.6, 21.6, 21.1, 18.3, 18.1, 13.2, −4.7, −4.8. IR ν_{max} ($CHCl_3$, cm^{-1}) 3072, 2958, 2934, 2864, 2247, 1636, 1469, 1368, 1252, 1083, 1011, 909. MS (*m/z*, I) 571 (MH^+, 19), 540 (MH^+ − OMe, 26), 538 (20), 440 (3), 438 (3), 405 (29). HRMS calcd for $C_{37}H_{67}O_2Si$ (MH^+) 571.4910, found 571.4913.

General Procedure for RCM: Preparation of Compound 26a. Ruthenium catalyst **16a** (40 mg, 0.11 mmol) was added to a solution of dienyne **21a** (13 mg, 0.16 mmol) in CH_2Cl_2 (20 mL), and the resulting mixture was refluxed under Ar for 2 h, concentrated under reduced pressure, and purified by flash chromatography (2% EtOAc/hexanes), giving 32 mg of compound **26a** [86%, R_f 0.5 (10% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.89 (1H, td, J = 10.3 and 7.7 Hz), 5.58 (1H, td, J = 10.2 and 6.5 Hz), 2.33 (1H, dd, J = 13.0 and 10.1 Hz), 0.91 (3H, s), 0.88 (3H, d, J = 6.5 Hz), 0.86 and 0.85 (6H, overlapped d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.0, 126.7, 78.5, 57.1, 51.8, 43.2, 43.0, 39.5, 36.9, 35.9, 35.2, 34.5, 30.0, 29.6, 28.1, 28.0, 27.8, 27.2, 23.7, 22.8, 22.5, 19.9, 18.4, 12.9. IR ν_{max} ($CHCl_3$, cm^{-1}) 3602, 3010, 2932, 2360, 2340, 1717, 1647, 1607, 1466, 1380, 1275, 1248, 1214, 1170, 1020. MS (*m/z*, I) 346 (M^+, 22), 331 (18), 277 (26), 264 (17). HRMS calcd for $C_{24}H_{42}O$ (M^+) 346.3236, found 346.3229. Elemental Anal. Calcd: C 83.16; H 12.22. Found: C 83.12; H 11.97.

Compound 26b. Using the conditions described for the preparation of **26a**, but with catalyst **16b** instead of **16a**, 24 mg of alcohol **26b** was obtained from **21b** [86%, R_f 0.4 (10% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.31 (1H, t, J = 7.4 Hz), 1.75 (3H, s), 0.9 (3H, s), 0.87 (3H, d, J = 6.1 Hz), 0.86 and 0.85 (6H, overlapped d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.5, 119.7, 78.9, 57.2, 51.8, 43.2, 43.0, 39.4, 37.6, 35.9, 35.2, 35.1, 33.3, 29.6, 29.1, 28.2, 28.0, 27.2, 25.1, 23.7, 22.7, 22.5, 19.8, 18.4, 12.9. MS (*m/z*, I) 361 (MH^+, 35), 343 ($MH^+ - H_2O$, 100), 327 (41). HRMS calcd for $C_{25}H_{44}O$ (M^+) 360.3392, found 360.3383. Elemental Anal. Calcd: C= 83.26%; H= 12.31%; found: C= 83.48%; H= 12.07%.

3-Ethenyl-6-(*tert*-butyldimethylsilyloxy)hexan-1-ol (29). Alcohol **28** (6.00 g, 26.00 mmol) was dissolved in *n*-butyl vinyl ether (60 mL), and $Hg(OAc)_2$ (4.15 g, 13.00 mmol) was added. The resulting solution was heated in a sealed flask at 160 °C for 26 h. The reaction mixture was cooled to 0 °C, and MeOH (20 mL) and $NaBH_4$ (1.20 g, 31.30 mmol) were added. After 10 min, H_2O was added and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure, giving a residue that upon flash chromatography (3% EtOAc/hexanes) afforded 233 mg of alcohol **29** [69%, R_f 0.3 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.52 (1H, m), 4.97 (2H, m), 3.58 (2H, m), 3.55 (2H, t, J = 6.3 Hz), 2.12 (1H, m), 1.98 (1H, m), 0.85 (9H, s), 0.006 (6H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.6, 114.9, 63.1, 60.9, 40.8, 37.8, 31.2, 30.2, 25.9, 18.3, −5.3. MS *m/z* 241 ($MH^+ - H_2O$, 35), 109 (100). HRMS calcd for $C_{14}H_{29}OSi$ ($MH^+ - H_2O$) 241.1988, found 241.1977.

Preparation of Alcohols 32a and 32b. Using the conditions described for the preparation of **26a**, 210 mg of a 1:1 diastereomeric mixture of (10*S*)-**26g** and (10*R*)-**26g** was obtained from **21g** [95%, R_f 0.4 (10% EtOAc/hexanes), colorless oil]. This mixture was dissolved in THF (5 mL), treated with TBAF (1 M in THF, 0.75 mL, 0.75 mmol), and stirred for 5 h at room temperature. A saturated solution of NH_4Cl was added and the resulting mixture was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated in vacuo, giving a residue that when flash chromatographed (20% EtOAc/hexanes) afforded 73 mg of **32a** and 69 mg of **32b**. **32a** [R_f 0.2 (25% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.58 (1H, q, J = 9.0 Hz), 5.26 (1H, t, J = 9.4 Hz), 3.59 (2H, t, J = 6.5 Hz), 0.89 (3H, s), 0.86 (3H, d, J = 6.6 Hz), 0.84 and 0.83 (6H, overlapped d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.2, 125.3, 76.9, 62.9, 57.0, 49.3, 45.2, 43.3, 41.0, 39.5, 35.8, 35.6, 35.1, 34.9, 32.2, 31.1, 29.6, 29.5, 27.9, 27.1, 23.7, 22.8, 22.5, 20.1, 18.3, 13.6. MS *m/z* 405 (MH^+, 30), 387 ($MH^+ - H_2O$, 93), 371 (50), 369 (37). HRMS calcd for $C_{27}H_{49}O_2$ (MH^+) 405.3733, found 405.3731. **32b** [R_f 0.3 (25% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.6 (2H, m), 3.6 (2H, t, J = 6.4 Hz), 0.9 (3H, s), 0.86 (3H, d, J = 6.6 Hz), 0.85 and 0.84 (6H, overlapped d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 138.4, 125.8, 79.0, 62.9, 57.1, 52.0, 43.1, 42.9, 39.4, 38.6, 37.6, 37.5, 35.8, 35.2, 35.1, 34.1, 33.3, 30.5, 28.1, 28.0, 27.1, 23.7, 22.7, 22.5, 19.8, 18.3, 12.8. MS *m/z* 405 (MH^+, 64), 387 ($MH^+ - H_2O$, 100). HRMS calcd for $C_{27}H_{49}O_2$ (MH^+) 405.3733, found 405.3735. Elemental Anal. Calcd: C 80.13; H 11.96. Found: C 79.87; H 12.08.

Aldehyde 33a. PDC (119 mg, 0.31 mmol) was added to a solution of alcohol **32a** (85 mg, 0.21 mmol) in CH_2Cl_2 (4 mL) containing molecular sieves. The reaction mixture was stirred under Ar for 2 h at room temperature and filtered through a Celite pad and the filtrate was washed with Et_2O. Concentration of the solvent in vacuo gave a residue that when flash chromatographed (15% EtOAc/hexanes) afforded 56 mg of **33a** [57%, R_f 0.4 (25% EtOAc/hexanes), white solid]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.73 (1H, s), 5.74−5.30 (2H, m), 0.89 (3H, s), 0.87 (3H, d, J = 6.5 Hz), 0.85 and 0.84 (6H, overlapped d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.5, 137.1, 126.9, 78.9, 57.1, 51.9, 43.1, 42.7, 41.9, 39.5, 38.3, 37.6, 37.4, 35.8, 35.1, 35.1, 33.9, 29.1, 28.1, 28.0, 27.1, 23.7, 22.7, 22.5, 19.8, 18.4, 12.8. MS *m/z* 402 (M^+, 36), 387 (25), 359 (21), 277 (82), 264 (100). HRMS calcd for $C_{27}H_{46}O_2$ (M^+) 402.3498, found 402.3496.

Aldehyde 33b. Prepared in the same way from alcohol **32b** as **33a** from **32a**. Yield 46 mg [66%, R_f 0.7 (50% EtOAc/hexanes), white solid]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.70 (1H, s), 5.61 (1H, q, J = 9.4 Hz), 5.23 (1H, t, J = 9.0 Hz), 0.9 (3H, s), 0.87 (3H, d, J = 6.5 Hz), 0.85 and 0.84 (3H, overlapped d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.5, 136.0, 126.4, 76.8, 56.9, 49.2, 45.2, 43.2, 42.4, 41.0, 39.4, 35.8, 35.4, 35.1, 34.9, 34.9, 29.6, 29.3, 28.0, 28.0, 27.0, 23.6, 22.8, 22.5, 20.1, 18.2, 13.6. MS *m/z* 402 (M^+, 40), 387 (12), 359 (30), 277 (72), 264 (100). HRMS calcd for $C_{27}H_{46}O_2$ (M^+) 402.3498, found 402.3493.

Vinyl Iodide 34a. A solution of NaHMDS (156 μL, 0.16 mmol) in THF was added under Ar to a suspension of iodomethyltriphenylphosphonium iodide (86 mg, 0.16 mmol) in the same solvent. The resulting solution was cooled to −60 °C and treated with HMPA (27 μL, 0.16 mmol) and aldehyde **33a** (50 mg, 0.12 mmol). After 30 min at room temperature, H_2O was added and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure, giving a residue that when flash chromatographed (5% EtOAc/hexanes) afforded 35 mg of the (*Z*)-vinyl iodide **34a** [72%, R_f 0.7 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.16 (2H, m), 5.58 (1H, dd, J = 18.2 and 8.5 Hz), 5.30 (1H, dd, J = 10.2 and 8.3 Hz), 2.56 (1H, br s), 0.93 (3H, s), 0.82 and 0.81 (6H, overlapped d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.1, 136.9, 125.5, 82.3, 76.9, 57.1, 49.4, 45.3, 43.3,

41.2, 39.5, 35.9, 35.2, 35.0, 34.3, 35.6, 34.3, 33.3, 29.7, 29.5, 28.0, 27.1, 23.7, 22.8, 22.5, 20.2, 18.3, 13.6. MS *m/z* 527 (MH^+, 7), 509 ($MH^+ - H_2O$, 17), 381 (18). HRMS calcd for $C_{28}H_{48}IO$ (MH^+) 527.2750, found 527.2746.

Vinyl Iodide 34b. Prepared from **33b** in the same way as **34a** from **33a** [37 mg, 70%, R_f 0.7 (20% EtOAc/hexanes), colorless oil]. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.16 (2H, m), 5.58 (2H, m), 0.92 (3H, s), 0.88 (3H, d, J = 6.6 Hz), 0.86 and 0.85 (6H, overlapped d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.9, 138.0, 126.0, 82.4, 79.0, 57.2, 52.1, 43.2, 43.0, 39.6, 38.5, 37.7, 37.4, 36.0, 35.5, 35.3, 35.3, 34.1, 32.8, 28.3, 28.1, 27.3, 23.8, 22.9, 22.7, 20.0, 18.5, 13.0. MS *m/z* 527 (MH^+, 2), 509 ($MH^+ - H_2O$, 13), 381 (21). HRMS calcd for $C_{28}H_{48}IO$ (MH^+) 527.2750, found 527.2762.

Tetracyclic Compound 36a. A solution of (*Z*)-vinyl iodide **34a** (65 mg, 0.12 mmol), $(PhP)_4Pd$ (13.7 mg, 0.012 mmol), and Et_3N (80 μL, 0.6 mmol) in MeCN (3.5 mL) was heated under Ar at 80 °C for 2 h. After cooling, a solution of HCl (10%) was added, and the resulting mixture was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4, and concentration under reduced pressure gave a residue that when flash chromatographed (2% EtOAc/hexanes) afforded 7 mg of the tetracyclic product **36a** [15%, R_f 0.7 (50% EtOAc/hexanes), white solid]. ^1H NMR ($CDCl_3$, 500 MHz) δ 5.63 (1H, m), 5.56 (1H, d, J = 9.7 Hz), 5.40 (1H, d, J = 12.3 Hz), 5.12 (1H, dd, J = 9.7 and 12.3 Hz), 2.80 (1H, t, J = 9.7 Hz), 1.96 (1H, dd, J = 13.3 and 7.2 Hz), 0.94 (3H, s), 0.89 (3H, d, J = 6.2 Hz), 0.86 and 0.85 (6H, overlapped d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 138.7, 131.4, 130.5, 126.9, 77.9, 57.3, 49.8, 47.7, 42.6, 39.5, 38.5, 37.7, 35.8, 35.8, 35.3, 32.5, 29.7, 28.9, 28.4, 28.0, 26.9, 26.2, 23.9, 22.8, 22.5, 20.2, 18.3, 14.0. MS *m/z* 399 (MH^+, 20), 381 ($MH^+ - H_2O$, 100), 365 (23), 338 (22). HRMS calcd for $C_{28}H_{47}O$ (MH^+) 399.3627, found 399.3622. Elemental Anal. Calcd: C 84.35; H 11.64. Found: C 84.68; H 11.42.

Tetracyclic Compound 36b. Under the conditions described for preparation of **36a**, 10 mg of iodide **36b** was obtained from **34b** [64%, R_f 0.5 (10% EtOAc/hexanes), white solid]. ^1H NMR ($CDCl_3$, 500 MHz) δ 5.72 (1H, m), 5.55 (1H, d, J = 12.0 Hz), 5.43 (1H, d, J = 9.9 Hz), 5.15 (1H, dd, J = 12.0 and 9.3 Hz), 3.41 (1H, t, J = 9.3 Hz), 2.23 (1H, m), 0.94 (3H, s), 0.88 (3H, d, J = 6.6 Hz), 0.85 and 0.84 (6H, overlapped d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 136.2, 133.5, 131.1, 126.3, 77.9, 57.1, 52.3, 46.5, 42.7, 39.5, 39.2, 38.6, 38.3, 35.8, 35.4, 35.3, 31.1, 31.0, 28.0, 27.1, 26.9, 25.0, 23.7, 22.8, 22.5, 19.7, 18.4, 14.2. MS *m/z* 399 (MH^+, 5), 381 ($MH^+ - H_2O$, 100), 379 (76), 365 (26). HRMS calcd for $C_{28}H_{47}O$ (MH^+) 399.3627, found 399.3609.

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Supporting Information Available: General methods, synthetic method for the preparation of **5**, **17a**, **18**, **20c**−**f**, **21b**−**f**, **26b^{Me}-h**, and **28**, and ^1H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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