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Ring Closing Metathesis/Fragmentation Route to (*Z*)-Configured Medium Ring Cycloalkenes. Total Synthesis of (±)-Periplanone C

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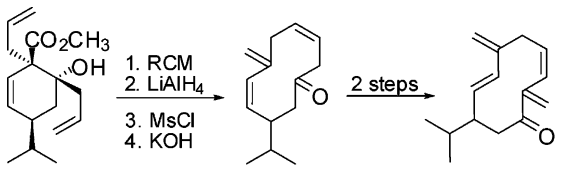

Periplanone C

The combination of ring closing metathesis and β-fragmentation offers an efficient entry into (*Z*)-configured medium ring cycloalkenes. The fragmentation step can be effected under anionic or radical conditions. The versatility of this method is demonstrated by the total synthesis of (±)-periplanone C—a macrocyclic pheromone of *Periplaneta americana*.

Introduction

Due to unfavorable enthalpic and entropic effects, the formation of medium- and large-sized rings is, in general, a more complex synthetic task, as compared to small and common ring closures.[1] As these structural units represent a frequent motif in numerous natural products and biologically active compounds, much effort has been invested in circumventing this problem.[2] Two principal synthetic approaches have been developed, which could be designated as the direct and the indirect one. The direct approach has been successfully applied using organotransition metal complexes, which are able to function, under mechanistically diverse conditions, as both reagents and templates, bringing the reacting centers (the termini) of the cyclization precursor into spatial proximity.[3] Alternatively, the indirect route, also known as the ring expansion method, involves the annulation of a new (small or common) ring to a monocyclic precursor, followed by the fragmentation of the central bond in the bicyclic intermediate;[4] the overall transformation results in the extension of the initial ring system and avoids complications associated with the macrocyclization.

The recent advent of catalysts for metathesis has had a considerable impact on the synthesis of medium- and large-sized rings.[5] Notably, the ruthenium and molybdenum carbene complexes of new generations proved capable of effecting traditionally difficult ring closures.[6] This property, combined with increased reactivity, improved functional group tolerance and stability toward oxygen and moisture, makes ring closing metathesis (RCM) an almost ideal tool for the direct macrocyclizations.[7] However, one important issue remained unsolved,

(1) (a) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 675−685. (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

(2) Review articles: (a) Molander, G. *Acc. Chem. Res.* **1998**, *31*, 603. Eight-Membered carbocycles: (b) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757. (c) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881. Eight- and nine-membered carbocycles: (d) Oishi, T.; Ohtsuka, Y. In *Studies in Natural Products Synthesis*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; Vol. 3, p 73. Lactones: (e) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777.

(3) Yet, L. *Chem. Rev.* **2000**, *100*, 2963.

(4) Review articles on radical methods: (a) Yet, L. *Tetrahedron* **1999**, *55*, 9349. (b) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091.

(5) Reviews on the development and various applications of the alkene metathesis reaction: (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (b) Schrock, R. R., Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (d) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (e) Blechert, S.; Connon, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

(6) For review articles on RCM, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141. (c) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75.

(7) For a short review on the application of RCM in the synthesis of medium-sized rings, see: (a) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. Review on the application of RCM macrocyclizations in the total synthesis of natural products: (b) Gradillas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086.

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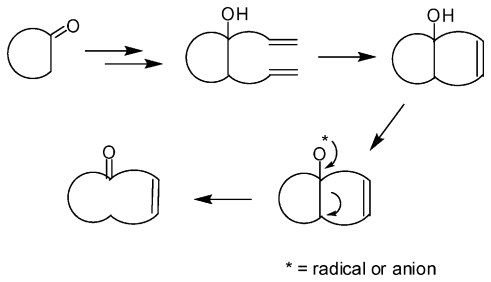
which is the control of alkene geometry in medium-sized and macrocyclic products. The stereochemical outcome of the reaction (i.e., *E/Z* ratio) is difficult to predict and, in general, impossible to modify. Most often, it appears to be substrate controlled, profoundly influenced by the ring size and substitution pattern.[8] Thus, even cyclooctene ring closure, which is normally expected to occur with (*Z*)-selectivity, under certain conditions, can afford an (*E*)-derivative exclusively.[9] Numerous examples are known where metathetic closures of medium-sized rings proceeded with (*E*)-selectivity, or nonselectively, both in the carbo- and heterocyclic series.[10] In some cases, it was shown that the stereochemical outcome of the reaction depends on the catalyst employed, where the more reactive, new generation catalysts favor the formation of thermodynamically controlled products; the less reactive ones promote the irreversible RCM, resulting in the kinetic control and, occasionally, inverted (*E/Z*)-ratio.[11] In larger rings (*E*)-products are usually favored,[12] where the degree of selectivity may depend on the reaction temperature[13] and solvent.[14] Although the application of RCM in the synthesis of (*E*)-alkene units in cyclic natural products has been recently reviewed,[15] (*Z*)-selective RCM remains elusive.

An indirect method, which circumvents the selectivity problem, relies on ring closing alkyne metathesis; the macrocyclic alkynes thus obtained can often be further reduced selectively to (*Z*)-cycloalkenes.[16] The catalysts for this type of transformation are, however, less developed than those for the alkene RCM.[17]

SCHEME 1



Results and Discussion

We set out to devise a method that would allow for a general, stereoselective synthesis of medium-sized (*Z*)-cycloalkenes, based on RCM. Our approach, delineated in Scheme 1, involves RCM of a cyclic substrate followed by fragmentation of a central bond in a condensed bicyclic intermediate. Several features of this indirect procedure should contribute to its efficiency: (a) the stereochemical constraints associated with small ring closure should secure the (*Z*)-configuration of the new alkene bond; (b) a RCM reaction that leads to a five-, six-, or seven-membered ring could be expected to proceed in a better yield, as compared to a direct medium-sized ring closure; (c) given the vast number of methods for small ring formation, as well as for nucleophilic and electrophilic introduction of alkenyl units, the RCM precursors should be readily available; (d) the fragmentation step could be performed under various conditions—anionic, radical—which adds to the versatility of the overall sequence. The annulation/fragmentation principle is well precedented and has been used in the synthesis of many complex natural products. However, we are aware of only two, relatively specific, examples of the RCM-based stereoselective ring expansion approach to medium-sized rings.[18] In a preliminary report, we disclosed our initial results on the RCM-based annulation/fragmentation route to medium-sized (*Z*)-cycloalkenes.[19] Here we wish to provide a full account of this study, together with some additional observations on the reactivity of intermediates.

The practical value of a synthetic method depends on the accessibility of the precursors. Scheme 2 represents, in a retrosynthetic format, several ways of assembling various types of cyclization/fragmentation precursors, in a few steps, starting from commercially available compounds. Variations in relative positions of the leaving group and the alkene bond formed by RCM give rise to diverse structural patterns of the expected cycloalken(on)e products.

To test the feasibility of the envisaged protocol, we endeavored to prepare several model compounds, and we first turned our attention toward the transformation of type 1, according to Scheme 2. A series of precursors were prepared in a straightforward way according to Scheme 3: allylation (or butenylation)

(8) However, attempts to generalize these observations have not met success; see, for example: Vassilikogiannakis, G.; Margaros, I.; Tofi, M. *Org. Lett.* **2004**, *6*, 205. Compare the conclusions from this reference to the following: Nicolaou, K. C.; Vassilikogiannakis, G.; Montagnon, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3276.

(9) Bourgeois, D.; Pancrazi, A.; Ricard, L.; Prunet, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 726.

(10) (*E*)-selective RCM of 10-membered rings. Cycloalkene: (a) Nevalainen, M.; Koskinen, A. M. P. *J. Org. Chem.* **2002**, *67*, 1554. Cycloalkene: (b) Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 588. Lactam: (c) Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334. Lactone: (d) Furstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061. 11-Membered rings: (e) El Sukkari, H.; Gesson, J. P.; Renoux, B. *Tetrahedron Lett.* **1998**, *39*, 4043. (f) Winkler, J. D.; Holland, J. M.; Kasparec, J.; Axelsen, P. H. *Tetrahedron* **1999**, *55*, 8199. (g) Arisawa, M.; Kato, C.; Kaneko, H.; Nishida, A.; Nakagawa, M. *J. Chem. Soc., Perkin Trans 1*, **2000**, 1873. (h) Furstner, A.; Muller, C. *Chem. Commun.* **2005**, 5583. 12-Membered rings: (i) Snider, B. B.; Song, F. *Org. Lett.* **2001**, *3*, 1817. (j) Wu, Y.; Liao, X.; Wang, R.; Xie, X.-S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245. (k) Couladouros, E. A.; Mihou, A. P.; Bouzas, E. A. *Org. Lett.* **2004**, *6*, 977. 14-Membered rings: (l) Furstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990. (m) Goldring, W. P. D.; Hodder, A. S.; Weiler, L. *Tetrahedron Lett.* **1998**, *39*, 4955.

(11) (a) Furstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehman, C. W.; Minott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061. (b) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145. (c) Furstner, A.; Schlede, M. *Adv. Synth. Catal.* **2002**, *344*, 657.

(12) Numerous examples in the 16-membered series come from synthetic studies toward epothilones, where undesired (*E*)-products usually predominate: (a) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Saurabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960. (b) Rivkin, A.; Cho, Y. S.; Gabarda, A. E.; Yoshimura, F.; Danishefsky, S. J. *J. Nat. Prod.* **2004**, *67*, 139. (c) Schinzer, D.; Limberg, A.; Bauer, A.; Bohm, O. M.; Cordes, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 523.

(13) Furstner, A.; Langemann, K. *Synthesis* **1997**, 792.

(14) Nakashima, K.; Ito, R.; Sono, M.; Tori, M. *Heterocycles* **2000**, *53*, 301.

(15) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826. Corrigendum: Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 3322.

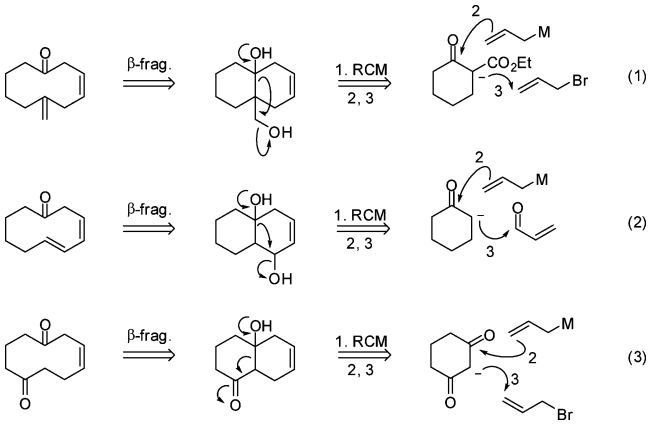
(16) (a) Furstner, A.; Turet, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 3462. (b) Furstner, A.; Mathes, C.; Grela, K. *Chem. Commun.* **2001**, 1057. (c) Furstner, A.; Grela, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1234.

(17) A review article on alkyne metathesis: Furstner, A.; Davies, P. W. *Chem. Commun.* **2005**, 2307.

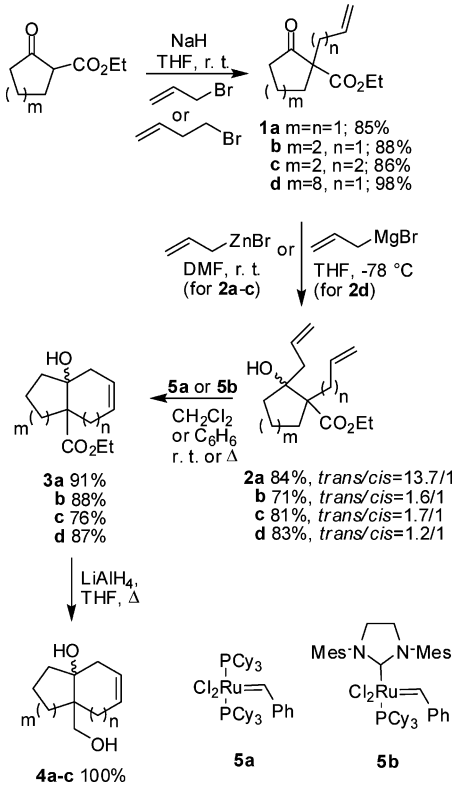
(18) (a) Mehta, G.; Kumaran, R. S. *Chem. Commun.* **2002**, 1456. (b) Rodriguez, J. R.; Castedo, L.; Mascarenas, J. L. *Chem.—Eur. J.* **2002**, *8*, 2923. See also: (c) Balskus, E. P.; Mendez-Andino, J.; Arbit, R. M.; Paquette, L. A. *J. Org. Chem.* **2001**, *66*, 6695. (d) Mendez-Andino, J.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 1263.

(19) Ivkovic, A.; Matovic, R.; Saicic, R. N. *Org. Lett.* **2004**, *6*, 1221.

SCHEME 2

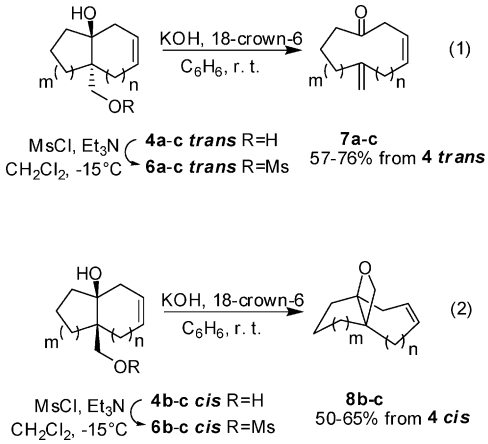


SCHEME 3



of cyclic β-ketoesters of various sizes,[20] followed by allylation of carbonyl group in **1**, afforded the required dienes **2a**−**d** in good yields. Cyclododecanone derivative **1d** proved unreactive toward the allylzinc reagent, and the Grignard reagent had to be used instead. With the exception of **2a**,[21] all the other dienes **2b**−**d** were obtained as mixtures of diastereoisomers, which were separated by column chromatography. No attempt was made to improve the stereoselectivity of the allylation, as the relationship between stereochemistry and reactivity of compound **2** was also one of the issues to be studied. On exposure to Ru catalyst **5a**[22] or **5b**,[23] all the substrates afforded the bicyclic

SCHEME 4



products **3a**−**d** in high yields. Upon submission to the cyclization/fragmentation cascade, the compounds **2a**−**c** were expected to yield 9−11-membered cycloalkenones with an additional *exo*-methylene double bond. Therefore, esters **3a**−**c** were reduced with lithium aluminum hydride into diols **4a**−**c**, thus setting the stage for the Grob fragmentation.

Diols **4a**−**c** were converted into the fragmentation precursors **6a**−**c** by regioselective mesylation and further used without purification (Scheme 4). After some experimentation, it was found that KOH in benzene, in the presence of 18-crown-6, gives clean fragmentation reactions with **6**.[24] It turned out that the outcome of the reaction depends on the relative stereochemistry of the hydroxyl and the leaving group in **6a**−**c**. Thus, **6a**−**c** ***trans*** all afforded the desired cycloalkenone products **7a**−**c** in good yields. No positional, nor stereochemical, isomerization of the alkene bond was observed. On the contrary, under the same reaction conditions, **6b**−**c** ***cis*** underwent cyclization, which gave rise to propellane-type oxetanes **8b**,**c**. This outcome is not surprising given that, as a rule, an anti-periplanar conformation of the reaction centers is required for the Grob fragmentation to proceed successfully.[25] The conclusion that can be drawn from these experiments is the following: if the fragmentation step is envisaged to be accomplished by Grob fragmentation, the synthesis of the fragmentation precursors has to be stereoselective, as, although the two stereocenters in **2**−**4** are not retained in the final products, the trans-configuration is required for the successful second step.

Alternatively, the fragmentation step can be accomplished under retro-aldol conditions. In this way, the mechanistic bifurcation associated with diastereoisomeric fragmentation precursors (as shown in Scheme 4) is avoided. Thus, when submitted to the action of potassium hexamethyldisilazide at −78 °C, **3d** afforded the macrocyclic product **9** in good yield (Scheme 5).[26] However, this possibility is restricted to large

(20) (a) Aburel, P. S.; Romming, C.; Ma, K.; Undheim, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1458. (b) Fraga, C. A. M.; Teixeira, L. H. P.; Menezes, C. M.; Sant'Anna, C. M. R.; Conceicao, M.; Ramos, K. V.; de Aquino Neto, F.; Barreiro, E. J. *Tetrahedron* **2004**, *60*, 2745.

(21) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705.

(22) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 110.

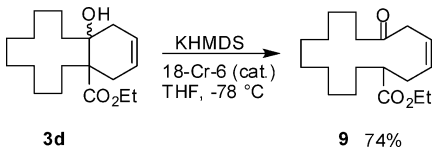
(23) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(24) Other bases, such as DBU, NaH, or metal alkoxides, were not successful.

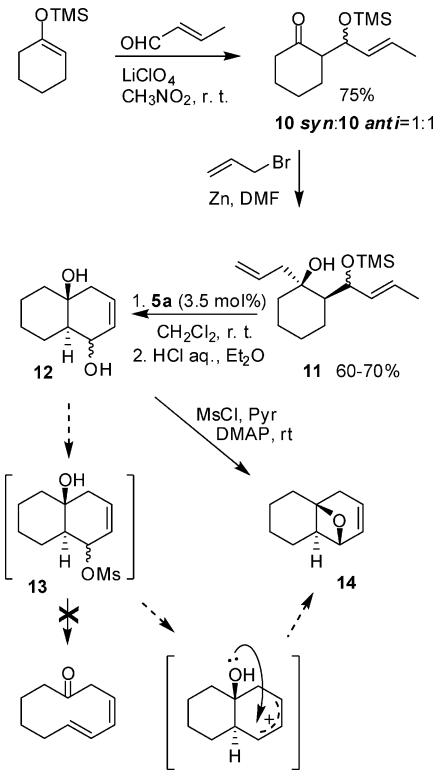
(25) However, examples are known where the fragmentation is successful even when this stereoelectronic requirement is not fulfilled; for a review article on Grob fragmentation, see: Weyerstahl, P.; Marschall, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 6, p 1041.

(26) Other bases, such as potassium ethoxide, potassium tert-butoxide, sodium hydride, DBU, potassium carbonate/18-crown-6, or potassium hydroxide/18-crown-6, were unsuccessful.

SCHEME 5



SCHEME 6

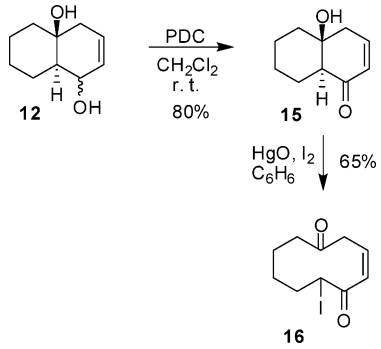


rings, where the equilibrium between the bicyclic precursor and the retro-aldol product favors the latter.[27]

For transformation 2, Scheme 2, the model compound **12** was prepared as displayed in Scheme 6. The reaction of cyclohexanone silylenol ether with crotonaldehyde, under modified Mukaiyama conditions, afforded the diastereomeric mixture of silylated aldol products **10** ***syn*** and **10** ***anti***.[28] Allylation of these compounds proceeded stereoselectively to give dienes **11**.[29] Upon submission to the first generation Grubbs' catalyst **5a**, both isomers of **11** cyclized to give, after deprotection, diols **12** ***syn*** and **12** ***anti***.[29] Surprisingly, when submitted to the conditions of Grob fragmentation, both diastereoisomers of **13** afforded the same oxetane derivative, **14**. Apparently, the allylic mesylate gave rise to a carbocation, which underwent substitution much faster than β-fragmentation.[30]

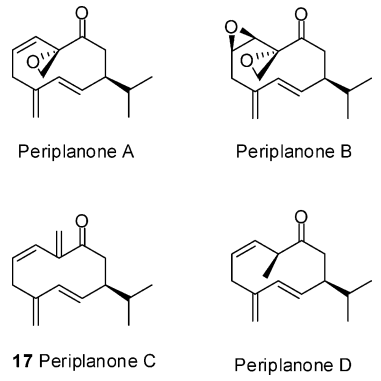
Therefore, in this case, we recurred to free-radical means to effect the fragmentation step (path 3, Scheme 2).[31] To this aim,

SCHEME 7



diol **12** was first oxidized to ketol **15** (Scheme 7). Upon submission to the conditions of the hypoiodite reaction, **15** was smoothly converted into the iodo-derivative **16**. Importantly, no isomerization of the alkene double bond took place under the reaction conditions.

These preliminary results encouraged us to apply the RCM/fragmentation method in the synthesis of more complex systems, such as macrocyclic semiochemicals.[32] We turned our attention toward a group of cyclic sesquiterpenes known as periplanones—sex pheromones of the American cockroach, *Periplaneta americana*—which attracted considerable interest from synthetic chemists.[33] The periplanone C **17** appeared to us as a challenging



target for the application of our method, as this germacrene derivative possesses four alkene units of both (*Z*)- and (*E*)-configuration, as well as a highly activated, conjugated *exo*-methylene group.[34] In addition, the total synthesis of periplanone

(27) In the case of compounds **3a**−**c**, the bicyclic system is thermodynamically favored and the fragmentation step cannot be performed as a simple retro-aldol reaction.

(28) Hirama, M.; Noda, T.; Takeishi, S.; Ito, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2645.

(29) The stereochemistry of compounds **11** and **12** was established in the following way: on oxidation with PDC both **12** ***syn*** and **12** ***anti*** were converted into the same ketone (**15**); this compound was then subjected to hydrogenation of the alkene bond over Pd/C to give the *trans*-decalone derivative described in the literature: Wharton, P. S.; Hiegel, G. A. *J. Org. Chem.* **1965**, *30*, 3254. See the Supporting Information for details.

(30) These results were obtained with the stereochemically defined isomers **12** ***syn*** and **12** ***anti***, purified by column chromatography and separately characterized. The whole sequence of reactions was also performed with the diastereomeric mixture, without the separation of the isomers, with similar results.

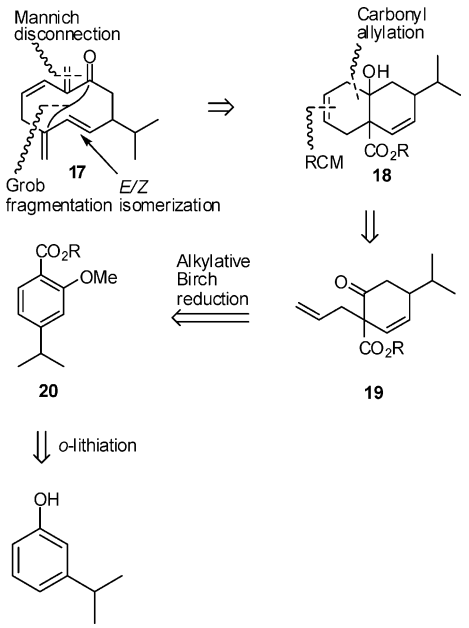
(31) (a) Saicic, R. N. *Tetrahedron Lett.* **1997**, *38*, 295. (b) Saicic, R. N.; Cekovic, Z. *J. Serb. Chem. Soc.* **1997**, *62*, 727.

(32) Czyzewska, E.; Oehlschlager, A. C. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1991; Vol. 8, p. 219.

(33) (a) Persoons, C. J.; Ritter, F. J.; Verwiel, P. E.; Hauptmenn, H.; Mori, K. *Tetrahedron Lett.* **1990**, *31*, 1747, and the references therein. (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, Germany, 1996; Chapters 13 and 21.

(34) Total syntheses of Periplanone C: (a) Shizuri, Y.; Matsunaga, K.; Tamaki, K.; Yamaguchi, S.; Yamamura, S. *Tetrahedron Lett.* **1988**, *29*, 1971. (b) McMurry, J. E.; Siemers, N. O. *Tetrahedron Lett.* **1994**, *35*, 4505. (c) Nishii, Y.; Watanabe, K.; Yoshida, T.; Takahashi, S.; Tanabe, Y. *Tetrahedron* **1997**, *53*, 7209.

SCHEME 8. Retrosynthetic Analysis of Periplanone C



C would also constitute formal syntheses of the periplanones A[35] and D.[36]

Our retrosynthetic analysis of periplanone C is outlined in Scheme 8. Mannich disconnection and selective alkene isomerization in **17** pave the way for the application of the fragmentation transform that converts the 10-membered ring into the unsaturated condensed bicycle **18**, on its turn obtainable by RCM. The precursor for the metathesis reaction could be prepared by the allylation of the carbonyl group in the unsaturated β-ketoester **19**; this latter compound would be assembled from the aromatic ester **20** by the alkylative Birch reduction.

The synthesis, displayed in Scheme 9, commenced with regioselective ortho-lithiation of the anisole derivative **21**, which, after carboxylation and esterification, gave ester **22**.[37] The Birch reduction of **22** with potassium, followed by quenching of the corresponding lithium enolate with allyl bromide[38] and *in situ* hydrolysis, furnished the required cyclic β-ketoester **23**, as a mixture of diastereoisomers in a 7:1 ratio. The allylation of the carbonyl group in **23** was performed with the allyl zinc reagent, prepared *in situ* in DMF, to give the RCM precursor **24** as a single stereoisomer. Upon exposure to 3 mol % of the first generation Ru-catalyst **5a**, diene **24** was smoothly converted into the bicyclic intermediate **25**. The scission of the central bond in the condensed bicycle **25** was envisioned to occur via Grob fragmentation (under ionic conditions). To this end, ester **25** was reduced with lithium aluminum hydride, followed by the regioselective mesylation of the primary hydroxyl group in **26**. Mesylate **27** was not purified but was submitted directly to the action of powdered potassium hydroxide in benzene, in the presence of 18-crown-6, to give the required cyclodecadienone intermediate **28** as a single geometrical isomer.

Although the stereochemical information contained in **23** and **24** are not transferred to the final product (the methoxycarbonyl bearing stereocenters in **23**−**26**, as well as the tertiary alcohol stereocenter in **24**−**26**, are destroyed in the fragmentation step), the stereochemical outcome of both reactions—Birch reductive alkylation of **22** and carbonyl allylation of **23**—is important for the success of synthesis. The predominant stereoisomer **23** in the Birch allylation reaction arises from the attack of the allyl bromide to the less hindered (trans to the isopropyl group) face of the intermediate ester enolate. The stereochemistry of the carbonyl allylation reaction of **23** can be predicted according to the model proposed by Molander.[21] Notably, of all four theoretically possible stereoisomeric products for **24** of the two reactions, only the stereoisomer **24** represented in Scheme 9 can be transformed into the desired macrocycle **28**. The model studies with the compound lacking the isopropyl side chain have shown that isomer **30**, with the cis stereochemistry of the hydroxyl and mesyloxy groups, affords the oxetane type product **31** under the conditions of the Grob fragmentation (Scheme 10).[39] In turn, when subjected to the conditions of RCM, **24** ***epi*** did not undergo cyclization, even after prolonged reaction times, as the trans-diaxial configuration of the two allyl groups precludes the cyclization of this diastereoisomer.

The sensitive nature of **28** severely restricted the choice of methods available for effecting the penultimate synthetic step—the regioselective isomerization of the (*Z*)-double bond of the conjugated diene moiety (Scheme 9). Clearly, both basic and acidic reagents had to be avoided, as the nonconjugated (*Z*)-olefinic bond would most probably suffer positional isomerization into the thermodynamically more stable conjugated enone.

Not unexpectedly, under the conditions of photochemical isomerization, **28** underwent transannular [2+2] photocycloaddition to yield the 8-*exo*-methylenetricyclo[4.4.0.0^{7,10}]decan-3-one derivative **32** (Scheme 11). Therefore, we envisaged to accomplish the necessary transformation by using a free radical methodology. Although extensively studied theoretically, radical isomerizations of alkenes have seldom been used in synthesis.[40] The *exo*-methylene group in **28** being the most reactive site for the radical attack, we hoped that the selective (*E*) → (*Z*) isomerization of the 1,3-butadiene unit would take place by a reversible addition/elimination of thiyl radicals, via the corresponding allylic radical. This approach was not devoid of pitfalls, however, as the related systems were reported to undergo positional and geometrical isomerization of nonconjugated olefinic bonds via the reversible radical addition, or hydrogen atom abstraction.[41] The latter reaction was especially threatening, in light of the known propensity of thiyl radicals to effect polarity reversal catalysis in hydrogen abstraction reactions.[42] In addition, the intermediary allylic radical could engage into a transannular cyclization, leading to unwanted isomerization of the nonconjugated alkene through the cyclopropylmethyl/butenyl rearrangement. Much to our pleasure, the

(35) Hofmeister, P.; Krieg, W.; Neudert, R.; Hauptmann, H. U.S. Patent 4,939,275.

(36) Biendl, M.; Hauptmann, H.; Sass, H. *Tetrahedron Lett.* **1989**, *30*, 2367.

(37) Shirley, D. A.; Harmon, T. E.; Cheng, C. F. *J. Organometal. Chem.* **1974**, *69*, 323.

(38) Hook, J. M.; Mander, L. N.; Woolias, M. *Tetrahedron Lett.* **1982**, *23*, 1095.

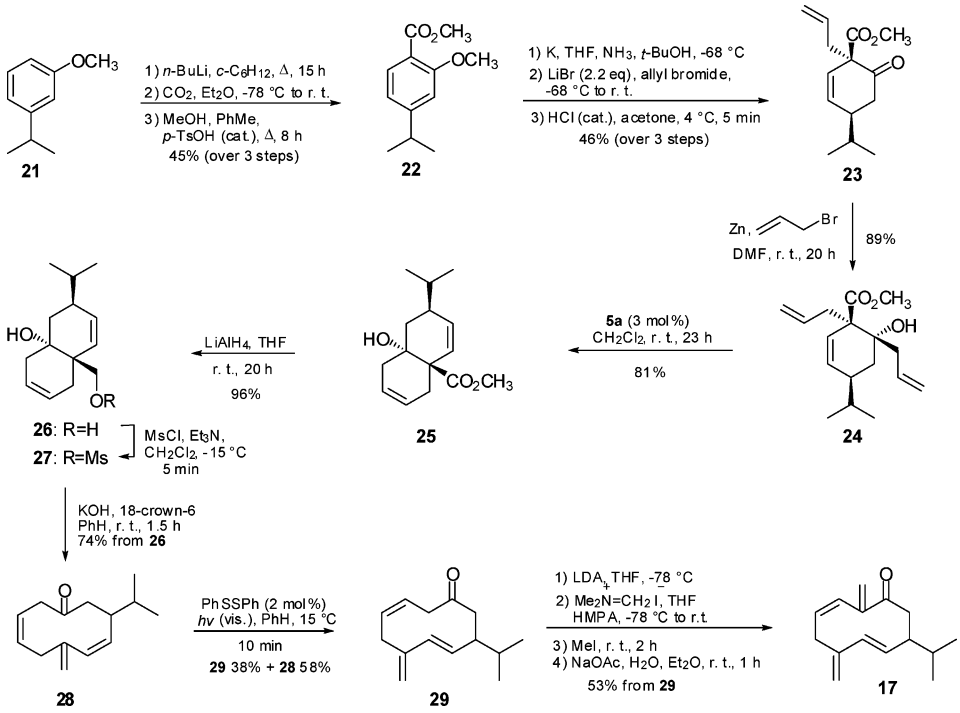
(39) In this case, the fragmentation step could be performed under radical conditions, which would require some additional steps though.

(40) A review article on the alkene (*E*)−(*Z*) isomerization: Dugave, C.; Demange, L. *Chem. Rev.* **2003**, *103*, 2475.

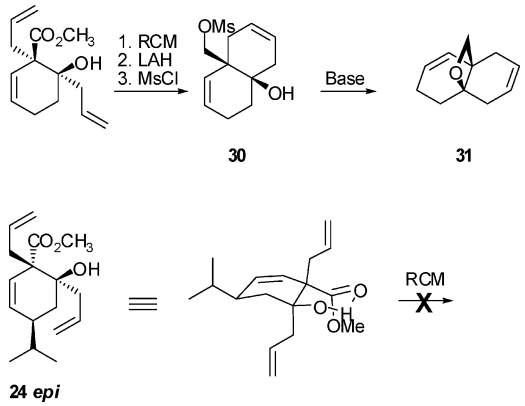
(41) Ferreri, C.; Costantino, C.; Perrotta, L.; Landi, L.; Mulazzani, Q. G.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **2001**, *123*, 4459.

(42) Triene **28** possesses four allylic hydrogen atoms sterically available for the abstraction, both electron-deficient (α to the carbonyl group) and electron-rich (α to the *exo*-methylene group). For a review article on polarity reversal catalysis in hydrogen abstraction reactions, see: Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25.

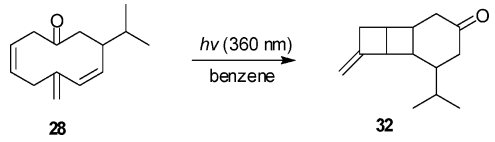
SCHEME 9. Synthesis of Periplanone C



SCHEME 10



SCHEME 11



irradiation of **28** with visible light in the presence of a catalytic amount of diphenyl disulfide brought about a smooth conversion into **29**. Although the equilibrium established at the isomer ratio **28**:**29** was 3:2, the yield calculated on the basis of the converted **28** was virtually quantitative, and the isomers could be easily separated by column chromatography on silver nitrate impregnated silica gel (SNIS).[43]

To the best of our knowledge, the regioselective Mannich methylenation of nonsymmetrical ketones possessing methylene groups in both α- and α′-positions was without literature precedent. We believed that the regioselectivity of the reaction with compound **29** should be secured by the synergetic action of two effects: the allylic activation of the α-position and the deactivation of the α′-position by the steric hindrance of the adjacent isopropyl group. Much to our disappointment, **29** proved unreactive toward TAMA—the reagent reported to effect methylenation under essentially neutral conditions.[44] Therefore, notwithstanding the risk of side reactions, the reaction had to be performed with the preformed metal enolate,[45] where the positional and configurational integrity of the (*Z*)-double bond was hoped to be preserved by operating at low temperature. Indeed, when the lithium enolate of **29** was treated with an excess of the Eschenmoser's reagent at −78 °C, the aminomethylation was followed by spontaneous elimination of dimethylamine to give periplanone C.[46] Its transformation into periplanones A and D has been reported previously.[35,36]

To summarize, we have shown that the combination of RCM and *β*-fragmentation offers an expedient, stereoselective entry into medium-sized (*Z*)-cycloalkenes. The fragmentation step can be effected under either anionic or radical conditions, which adds to the versatility of the procedure, whose applicability is demonstrated in the total synthesis of (±)-periplanone C.

Experimental Section

Ethyl *cis*- and *trans*-2-Hydroxy-1,2-bis(2-propenyl)cyclododecanecarboxylate (2d *cis* and 2d *trans*). To a cold (−78 °C) solution of ethyl 1-(2-propenyl)-2-oxocyclododecanecarboxylate (400 mg, 1.36 mmol) in diethyl ether (8 mL) was added a solution of allylmagnesium bromide (3.36 g, 23 mmol) in diethyl ether (20 mL) dropwise with stirring under an argon atmosphere. Upon completion of the reaction, water (10 mL) was added, and the

(43) A review article on SNIS: Williams, C. M.; Mander, L. N. *Tetrahedron* **2001**, *57*, 425.

(44) (a) Gras, J.-L. *Tetrahedron Lett.* **1978**, 2111. (b) Gras, J.-L. *Org. Synth. Coll. Vol. VII*, 332.

(45) Roberts, J. L.; Borromeo, P. S.; Poulter, C. D. *Tetrahedron Lett.* **1977**, 1621.

(46) ^{1}H NMR and IR spectra identical to those reported for the naturally occurring compound (ref 36). ^{13}C NMR spectrum identical to the spectrum previously reported in ref 34c.

reaction mixture was allowed to reach room temperature (rt). Extraction with dichloromethane (3 × 50 mL), followed by drying over anhydrous magnesium sulfate, concentration under reduced pressure, and purification by low-pressure liquid chromatography (LPLC) (eluent: 1.25% ethyl acetate in petroleum ether, with 0.75% triethylamine added to the eluent) afforded 140 mg (37%) of *trans*-ethyl 1,2-diallyl-2-hydroxycyclododecanecarboxylate (**2d *trans***) (eluted first), followed by 240 mg (46%) of *cis*-ethyl 1,2-diallyl-2-hydroxycyclododecanecarboxylate (**2d *cis***).

Physical data for **2d *trans***. Colorless oil. IR (film, cm^{-1}): 2977, 2927, 2863, 1696, 1446, 1221, 1161, 913. ^1H NMR (δ): 5.83−6.07 (m, 2H); 4.99−5.14 (m, 4H); 4.18 (q, J = 7.1, 2H); 3.74 (s, 1H, O*H*); 2.27−2.69 (m, 4H); 1.88−1.16 (m, 23H). ^{13}C NMR (δ): 176.7 (C); 136.3 (CH); 134.9 (CH); 117.7 (CH_2); 117.1 (CH_2); 77.7 (C); 60.7 (CH_2); 57.1 (C); 42.3 (CH_2); 38.1 (CH_2); 34.3 (CH_2); 33.5 (CH_2); 26.9 (CH_2); 26.4 (CH_2); 24.8 (CH_2); 24.5 (CH_2); 23.5 (CH_2); 23.3 (CH_2); 23.0 (CH_2); 21.5 (CH_2); 14.1 (CH_3). HRMS (ESI): calcd for $C_{21}H_{36}O_3Na$, 359.2562; found, 359.2563.

Physical data for **2d *cis***. Colorless oil. IR (film, cm^{-1}): 2980, 2929, 2864, 1721, 1471, 1446, 1220, 1160, 1029, 1001, 915. ^1H NMR (δ): 6.05−5.68 (m, 2H); 5.18−4.98 (m, 4H); 4.15, (J = 6.8, 2H); 3.09 (s, 1H, O*H*); 2.65−2.84 (dd, J_1 = 14.3, J_2 = 7.2, 1H); 2.44−2.60 (dd, J_1 = 14.3, J_2 = 7.2, 1H); 2.30−2.44 (dd, J_1 = 14.3, J_2 = 7.2, 1H); 1.90−2.20 (m, 2H); 1.14−1.89 (m, 22H). ^{13}C NMR (δ): 176.5 (C); 135.5 (CH); 134.5 (CH); 118.0 (CH_2); 117.8 (CH_2); 77.2 (C); 60.8 (CH_2); 58.2 (C); 41.9 (CH_2); 34.7 (CH_2); 34.6 (CH_2); 30.2 (CH_2); 26.6 (CH_2); 26.4 (CH_2); 24.1 (CH_2); 24.0 (CH_2); 23.0 (CH_2); 22.6 (CH_2); 21.4 (CH_2); 20.9 (CH_2); 14.1 (CH_3). HRMS (ESI): calcd for $C_{21}H_{36}O_3Na$, 359.2562; found, 359.2547.

Ethyl *cis*- and *trans*-Bicyclo[4.4.0]dec-3-en-6-ol-1-carboxylate (3b *cis* and 3b *trans*) (Ring Closing Metathesis of 2b). To a solution of compound **2b** (660 mg, 2.62 mmol) in dichloromethane (15.6 mL), previously deaerated in an ultrasonic bath under a stream of argon, was added catalyst **5a** (22.2 mg, 26 μmol, 0.75 mol %), and the reaction mixture was heated to reflux under an argon atmosphere. After 1.5 h, an additional amount of catalyst **5a** (15.2 mg, 18 μmol) was added, and after 2.5 h, a second supplementary amount of catalyst **5a** (15.2 mg, 18 μmol) was added. After 6 h, the reaction was complete. The reaction was allowed to cool, lead tetraacetate (46.6 mg, 0.105 mmol) was added, and the mixture was stirred at rt for 7 h. The suspension was filtered through a short pad of silica, the pad was washed with dichloromethane and ethyl acetate, and the combined organic extract was concentrated under reduced pressure and purified by dry-flash chromatography (eluent: toluene:ethyl acetate = 97:3) to give 293 mg (50%) of the title compound **3b** as a mixture of diastereoisomers. The diastereoisomers were separated by LPLC (eluent: petroleum ether: ethyl acetate = 95:5) to give 128 mg of **3b *cis*** and 146 mg of **3b *trans***.

When the reaction was performed with catalyst **5b**, in boiling benzene, the title compound was isolated in 88% yield (as a mixture of diastereoisomers).

Physical data for **3b *cis***. Colorless oil. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 70.04; H, 9.29. IR (film, cm^{-1}): 3510, 3028, 2942, 2866, 1702, 1451, 1394, 1299. ^1H NMR (δ): 5.52−5.64 (m, 2H); 4.48 (bs, 1H); 4.18 (q, J = 7.0, 2H); 2.22−2.62 (m, 4H); 1.98−2.10 (m, 2H); 1.72−1.78 (m, 2H); 1.35−1.64 (m, 4H); 1.27 (t, J = 7.0, 3H). ^{13}C NMR (δ): 178.6 (C); 124.6 (CH); 123.0 (CH); 70.6 (C); 60.7 (CH_2); 49.1 (CH_2); 34.8 (2 × CH_2); 31.8 (CH_2); 30.6 (CH_2); 21.7 (2 × CH_2); 14.0 (CH_3).

Physical data for **3b *trans***. Colorless oil. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.20; H, 9.31. IR (KBr, cm^{-1}): 3545, 3026, 2958, 2933, 2860. ^1H NMR (δ): 5.54−5.70 (m, 2H), 4.11 (q, J = 7.0, 1H); 4.09 (q, J = 7.0, 1H); 2.75−2.90 (m, 1H); 2.45 (dd, J_1 = 16.8, J_2 = 4.0, 1H); 1.52−2.24 (m, 11H); 1.23 (t, J = 7.0, 3H). ^{13}C NMR (δ): 175.0 (C); 125.3 (CH); 124.9 (CH); 70.1 (C); 60.1 (CH_2); 49.5 (C); 38.4 (CH_2); 34.2 (CH_2); 33.1 (CH_2); 32.1 (CH_2); 22.8 (CH_2); 21.3 (CH_2); 14.1 (CH_3).

Ethyl *trans*-12-Hydroxybicyclo[10.4.0]hexadec-14-ene-1-carboxylate (3d *trans*). To a solution of **2d *trans*** (150 mg, 0.446 mmol) in deaerated dichloromethane (3 mL) was added catalyst **5a** (11 mg, 13.4 μmol), and the reaction mixture was stirred at rt for 4 h under an argon atmosphere. Lead tetraacetate (9 mg, 0.02 mmol) was added, and the mixture was stirred at rt overnight. The suspension was filtered through a short pad of silica, the pad was washed with dichloromethane, and the combined organic extract was concentrated under reduced pressure and purified by dry-flash chromatography (eluent: petroleum ether:ethyl acetate = 975:25) to give 120 mg (87%) of the title compound **3d *trans***.

Physical data for **3d *trans***. Colorless oil. IR (film, cm^{-1}): 2929, 2862, 1725, 1180. ^1H NMR (δ): 5.77−5.65 (m, 1H); 5.49−5.61 (m, 1H); 4.10 (q, J = 7.1, 2H); 2.42−2.68 (m, 2H); 2.16−2.32 (m, 1H); 0.92−2.07 (m, 25H). ^{13}C NMR (δ): 174.9 (C); 126.4 (CH); 124.8 (CH); 73.2 (C); 60.0 (CH_2); 52.8 (C); 37.3 (CH_2); 35.5 (CH_2); 33.7 (CH_2); 32.9 (CH_2); 26.8 (CH_2); 26.2 (CH_2); 26.1 (CH_2); 23.7 (CH_2); 23.4 (CH_2); 23.1 (CH_2); 22.1 (CH_2); 21.4 (CH_2); 14.2 (CH_3). HRMS (ESI): calcd for $C_{19}H_{32}O_3Na$, 331.2249; found, 331.2241.

(*Z*)-6-Methylenecyclonon-3-ene-1-one (7a) (Ring Expansion by Grob Fragmentation). Mesyl chloride (56 μL, 0.71 mmol) was added to a cold (−15 °C) solution of **4a** (100 mg, 0.59 mmol) and triethylamine (125 μL, 0.89 mmol) in dichloromethane (4.3 mL) with stirring under an argon atmosphere. After 25 min, diethyl ether (6 mL) and saturated aqueous $NaHCO_3$ (6 mL) were added and vigorous stirring was continued for 10 min. The aqueous layer was extracted with ether, the combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give the crude mesylate **6a *trans***, which was used in the next step without purification.

18-Crown-6 (550 mg, 2.1 mmol) was added to a benzene (15.4 mL) solution of mesylate **6a *trans*** from the previous step. To this solution was added finely powdered KOH (84.6 mg, 1.51 mmol), and the mixture was stirred for 4.5 h at rt. Upon dilution with dichloromethane and water, the layers were separated, the aqueous layer was extracted with dichloromethane, and the combined organic extract was dried over anhydrous $MgSO_4$ and carefully concentrated under reduced pressure (the compound is highly volatile). The mixture was purified by dry-flash chromatography (eluent: pentane: diethyl ether = 95:5) to give 51 mg (57%) of the title compound **7a**. An analytical sample of **7a** was obtained by preparative gas chromatography.

Physical data for **7a**. Light yellow oil. IR (film, cm^{-1}) 3071, 3023, 2931, 2860, 1704, 1602, 1444. ^1H NMR (δ): 5.63−5.79 (m, 2H); 4.82 (d, J = 1.1, 2H); 3.18 (dd, J_1 = 15.4, J_2 = 9.2, 2H); 2.92 (dd, J_1 = 15.4, J_2 = 9.2, 2H); 2.47−2.53 (m, 2H); 2.10−2.20 (m, 2H) 1.80−1.92 (m, 2H). ^{13}C NMR (δ): 147.0 (C); 131.9 (CH); 123.4 (CH); 113.6 (CH_2); 42.6 (CH_2); 42.6 (CH_2); 35.0 (CH_2); 34.2 (CH_2); 24.6 (CH_2); the peak corresponding to the carbonyl group was not detected under the recording conditions. HRMS (ESI): calcd for $C_{10}H_{14}ONa$, 173.0942; found, 173.0945.

11-Oxatricyclo[4.4.2.0^{1,6}]dodec-3-ene (8b). Mesyl chloride (50 μL, 0.66 mmol) was added to a cold (−15 °C) solution of **4b *cis*** (100 mg, 0.55 mmol) and triethylamine (115 μL, 0.82 mmol) in dichloromethane (3.9 mL) with stirring under an argon atmosphere. After 30 min, diethyl ether (6 mL) and saturated aqueous $NaHCO_3$ (6 mL) were added and the mixture was vigorously stirred for 10 min. The aqueous layer was extracted with ether, the combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give the crude mesylate **6b *cis***, which was used in the next step without purification.

18-Crown-6 (461 mg, 1.75 mmol) was added to a benzene (12.9 mL) solution of mesylate **6b *cis*** from the previous step. To this solution was added finely powdered KOH (70 mg, 1.25 mmol), and the mixture was stirred for 4.5 h at rt. Upon dilution with dichloromethane and water, the layers were separated, the aqueous layer was extracted with dichloromethane, and the combined organic

extract was dried over anhydrous $MgSO_4$ and carefully concentrated under reduced pressure (the compound is highly volatile). The mixture was purified by dry-flash chromatography (eluent: pentane:diethyl ether = 9:1) to give 41 mg (50%) of the title compound **8b**.

Physical data for **8b**. Light yellow liquid. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.21; H, 10.06. IR (film, cm^{-1}): 3034, 2918, 2869, 1452, 1382, 1343, 1269. ^1H NMR (δ): 5.94−6.10 (m, 2H); 4.35 (d, J = 5.5, 1H); 4.12 (d, J = 5.5, 1H); 2.16−2.26 (m, 1H); 1.19−2.06 (m, 11H). ^{13}C NMR (δ): 128.2 (CH); 127.0 (CH); 87.4 (C); 75.5 (CH_2); 47.3 (C); 36.0 (CH_2); 33.3 (CH_2); 32.9 (CH_2); 29.9 (CH_2); 17.8 (CH_2); 17.0 (CH_2).

(*Z*)-Ethyl 6-Oxocyclohexadec-3-enecarboxylate (9) (Ring Expansion by a Retro-aldol Reaction). KHMDS (130 μL of the 0.5 M solution in THF, 64.8 μmol, 2 equiv) was added to a cold (−78 °C) solution of **3d** (10 mg, 32.4 μmol, equimolar mixture of cis and trans isomers) and 18-crown-6 (catalytic amount) in THF (1 mL), and the resulting solution was stirred for 20 min under an argon atmosphere. The reaction was quenched by the addition of water (1 mL) and extracted with dichloromethane (3 × 10 mL); the organic layer was washed with water (10 mL), dried over anhydrous $MgSO_4$, concentated under reduced pressure, and the residue was purified by dry-flash chromatography (eluent: petroleum ether:ethyl acetate = 95:5) to give 7.4 mg (74%) of the title compound **9**.

Physical data for **9**. Colorless oil. Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 74.25; H, 10.59. IR (film, cm^{-1}): 2931, 2859, 1726, 1454, 1374, 1266, 1172, 1038. ^1H NMR (δ): 5.48−5.75 (m, 2H); 4.16 (q, J = 7.0, 2H); 3.36 (dd, J_1 = 17.0, J_2 = 8.2, 1H); 3.06 (dd, J_1 = 17.0, J_2 = 5.2, 1H); 2.22−2.51 (m, 5H); 1.40−1.80 (m, 4 H); 1.30−1.40 (br s, 14H); 1.27 (t, J = 7.0, 3H). ^{13}C NMR (δ): 208.9 (C); 175.7 (C); 130.0 (CH); 123.4 (CH); 60.2 (CH_2); 44.4 (CH); 41.7 (CH_2); 41.2 (CH_2); 30.2 (CH_2); 29.4 (CH_2); 26.9 (CH_2); 26.8 (CH_2); 26.1 (CH_2); 25.8 (CH_2); 25.6 (CH_2); 25.4 (CH_2); 22.6 (CH_2); 14.2 (CH_3); two peaks of methylene carbon atoms are superimposed.

(*Z*)-10-Iodocyclodec-2-ene-1,5-dione (16) (Ring Expansion by Radical Fragmentation). Mercuric oxide (88.5 mg, 0.41 mmol) and iodine (104 mg, 0.41 mg) were added to a solution of **15** (34 mg, 0.205 mmol) in benzene (8 mL). The reaction mixture was deaerated with a stream of argon and irradiated with a Xenophot 250 W focalized light with vigorous stirring. After 20 min, the reaction mixture was filtered, diluted with dichloromethane (70 mL), washed with aqueous sodium thiosulfate (2 × 5 mL) and water (10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by dry-flash chromatography (eluent: 20% ethyl acetate in hexanes) gave 39 mg (65%) of the title compound **16**.

Physical data for **16**. Colorless plates, mp 93.5−94 °C. Anal. Calcd for $C_{10}H_{13}IO_2$: C, 41.12; H, 4.49. Found: C, 41.08; H, 4.29. IR (KBr, cm^{-1}): 2939, 2858, 1713, 1690, 1626, 1464, 1395, 1292, 1243, 1198, 1137, 1102. ^1H NMR (δ): 7.12 (d, J = 12.0, 1H); 6.11−6.22 (m, 1H); 4.53 (dd, J_1 = 3.7, J_2 = 10.8, 1H); 3.68 (dd, J_1 = 10.4, J_2 = 15.8, 1H); 3.20 (dd, J_1 = 7.1, J_2 = 15.8, 1H); 2.16−2.58 (m, 4H); 1.56−1.68 (m, 4H). ^{13}C NMR (δ): 200.7; 200.2; 134.7; 129.7; 41.8; 39.2; 33.7; 31.2; 28.3; 21.5.

Total Synthesis of (±)-Periplanone C Methyl *cis*-1-Allyl-*r*-4-isopropyl-6-oxocyclohex-2-enecarboxylate (23) (Reductive Alkylation of 22).[47] To a cold (−68 °C) solution of **22** (916 mg, 4.4 mmol) in liquid ammonia (36 mL), THF (18 mL), and *tert*-butanol was added potassium metal (400 mg, 10.256 mmol) in small pieces with stirring. After the addition was complete, the reaction mixture was stirred for an additional 15 min, and then LiBr (840 mg, 9.66 mmol) was added in one portion when the reaction turned from deep blue to yellow. After 15 min, allyl bromide (2.12 g, 17.6 mmol) was added, the reaction mixture was stirred 30 min at that temperature, and then the cooling bath was removed and the ammonia left to evaporate. The reaction mixture was diluted with a saturated aqueous NH_4Cl solution (30 mL) and extracted with dichloromethane (3 × 50 mL). The organic extract was dried over anhydrous Na_2SO_4, filtered off, and concentrated under reduced pressure. The crude residue (967 mg) was purified by dry-flash chromatography (eluent: petroleum ether:acetone = 985:15) to obtain the corresponding enol ether (methyl 1-allyl-4-isopropyl-2-methoxycyclohexa-2,5-dienecarboxylate, 714 mg). This compound was dissolved in acetone (5 mL), cooled to 4 °C, and concentrated HCl (1 mL) was added with stirring. After 1 min, the reaction mixture was neutralized by careful addition of $NaHCO_3$ (990 mg), concentrated under reduced pressure, diluted with water, and extracted with dichloromethane (3 × 50 mL). The organic extract was dried over anhydrous Na_2SO_4, filtered off, and concentrated under reduced pressure. Purification of the crude product (675 mg) by dry-flash chromatography (eluent: petroleum ether:diethyl ether = 96:4) afforded the title compound **23** (408 mg, 39%), followed by the more polar *trans*-isomer (methyl *cis*-1-allyl-*r*-4-isopropyl-6-oxocyclohex-2-enecarboxylate, 60 mg, 6%).

Alternatively, the transmetalation with LiBr can be omitted (the rest of the experimental procedure remains identical), which results in an improved overall yield (56%) but with lower stereoselectivity (cis:trans = 4:1).

Physical data for **23**. Pale-yellow oil. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.93; H, 8.74. IR (film, cm^{-1}): 2960, 2876, 1740, 1722, 1642, 1435, 1233, 1133. ^1H NMR (δ): 5.94 (dd, J_1 = 10.0, J_2 = 2.2, 1H); 5.24 (dd, J_1 = 10.0, J_2 = 2.2, 1H); 5.72−5.55 (m, 1H); 5.13−5.02 (m, 2H); 3.71 (s, 3H); 2.71 (dd, J_1 = 13.7, J_2 = 7.5, 1H); 2.58 (dd, J_1 = 13.7, J_2 = 6.9, 1H); 2.53−2.35 (m, 3H); 1.81−1.68 (m, 1H); 0.94 (d, J = 2.0, 3H); 0.91 (d, J = 2.1, 3H). ^{13}C NMR (δ): 206.4 (C); 170.9 (C); 132.8 (CH); 132.7 (CH); 128.0 (CH); 118.8 (CH_2); 59.7 (C); 52.5 (CH_3); 43.8 (CH); 41.0 (CH_2); 38.7 (CH_2); 31.8 (CH); 19.1 (CH_3); 18.6 (CH_3).

Methyl *cis*-1-*trans*-6-Diallyl-6-hydroxy-*r*-4-isopropylcyclohex-2-enecarboxylate (24). To a solution of **23** (194 mg, 0.822 mmol) and allyl bromide (149 mg, 1.23 mmol) in DMF (0.64 mL) was added Zn powder (80 mg, 1.22 mmol) in one portion with stirring. The reaction mixture was stirred for 20 h, then diluted with saturated aqueous NH_4Cl (10 mL), and extracted with dichloromethane (3 × 50 mL). The organic extract was washed with water, dried over anhydrous Na_2SO_4, filtered off, and concentrated under reduced pressure. Purification of the crude residue (225 mg) by dry-flash chromatography (eluent: petroleum ether:ethyl acetate = 97:3) afforded the title compound **24** (204 mg, 89%).

Physical data for **24**. Colorless oil. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H 9.41. Found: C, 73.16; H, 9.15. IR (film, cm^{-1}): 3539, 2957, 1725, 1640, 1438, 1218, 1001. ^1H NMR (δ): 6.01−5.60 (m, 4H); 5.21−5.08 (m, 4H); 3.67 (s, 3H); 2.87 (dd, J_1 = 13.9, J_2 = 5.8, 1H); 2.61 (dd, J_1 = 14.2, J_2 = 6.7, 1H); 2.37 (dd, J_1 = 13.9, J_2 = 8.8, 1H); 2.19−2.05 (m, 2H); 1.98 (s, 1H); 1.84−1.66 (m, 2H); 1.57 (dd, J_1 = 13.7, J_2 = 10.0, 1H); 0.94 (s, 3H); 0,91 (s, 3H). ^{13}C NMR (δ): 174.0 (C); 134.8 (CH); 133.6 (CH); 131.5 (CH); 126.8 (CH); 119.1 (CH_2); 118.7 (CH_2); 73.5 (C); 55.4 (C); 51.9 (CH_3); 41.5 (CH_2); 38.5 (CH); 36.9 (CH_2); 32.6 (CH_2); 31.4 (CH); 19.5 (CH_3); 19.4 (CH_3).

***trans*-1-Hydroxy-*cis*-6-methoxycarbonyl-*r*-9-isopropyl-bicyclo-[4.4.0]deca-3,7-diene (25).** Benzylidenebis(tricyclohexylphosphine)-dichlororuthenium (**5a**) (6 mg, 7.2 μmol) was added to a solution of **24** (204 mg, 0.734 mmol) in dichloromethane (3.7 mL), and the resulting mixture was stirred at room temperature for 15 h. A new portion of **5a** (12 mg, 14.4 μmol) was added, and the mixture was stirred for an additional 8 h, when TLC indicated that the reaction was complete. Lead tetraacetate (14.6 mg, 32.9 μmol) was added, and the resulting suspension was stirred for 12 h. The reaction mixture was filtered through a plug of silica (1 g), the plug was washed with dichloromethane (4 × 3 mL), and the organic extract was concentrated under reduced pressure. Purification by dry-flash

(47) Hook, J. M.; Mander, L. N.; Woolias, M. *Tetrahedron Lett.* **1982**, *23*, 1095.

chromatography (eluent: petroleum ether:ethyl acetate = 95:5) afforded the title compound **25** (148 mg, 81%).

Physical data for **25**. Colorless oil. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.79; H, 8.97. IR (film, cm^{-1}): 3525, 2957, 1732, 1648, 1462, 1440, 1373, 1277, 1176, 1030. ^{1}H NMR (δ): 5.83−5.77 (m, 1H); 5.75−5.58 (m, 2H); 5.48 (dd, J_1 = 10.0, J_2 = 2.2, 1H); 3.61 (s, 3H); 2.79−2.57 (m, 2H); 2.39−1.97 (m, 5H); 1.79−1.63 (m, 2H); 0.91 (d, J = 5.5, 3H); 0.87 (d, J = 5.5, 3H). ^{13}C NMR (δ): 132.9 (CH); 127.9 (CH); 125.9 (CH); 125.2 (CH); 70.4 (C); 51.9 (CH_3); 49.8 (C); 39.0 (CH); 37.0 (CH_2); 33.3 (CH_2); 31.5 (CH); 31.4 (CH_2); 19.4 (CH_3); 19.0 (CH_3). The peak of the ester carbonyl was not observed under the recording conditions.

(3*Z*,7*Z*)-9-Isopropyl-6-methylenecyclodeca-3,7-dienone (28). Methanesulfonyl chloride (49 mg, 0.426 mmol) was added to a cold (−15 °C) solution of **26** (70 mg, 0.355 mmol) and triethylamine (54 mg, 0.532 mmol) in dichloromethane (1.8 mL) with stirring. After 1 min, saturated aqueous $NaHCO_3$ (0.5 mL) was added and the reaction mixture was diluted with diethyl ether (100 mL). The organic extract was thoroughly washed with saturated aqueous $NaHCO_3$ (4 × 10 mL, 10 min every washing), water, and brine; dried over anhydrous $MgSO_4$; filtered off; and evaporated under reduced pressure. The crude product **27** (colorless oil, 109 mg) was used in the next step without further purification. To a solution of **27** and 18-crown-6 (332 mg; 1.26 mmol) in benzene (8.8 mL) was added powdered KOH (50.4 mg, 0.9 mmol) with stirring. After 90 min, saturated aqueous NH_4Cl (8 mL) was added, the reaction mixture was extracted with dichloromethane (5 × 20 mL), and the organic extract was washed with water, dried over anhydrous Na_2SO_4, filtered off, and concentrated under reduced pressure. Purification of the crude residue (100 mg) by dry-flash chromatography (eluent: petroleum ether:acetone = 96:4) afforded the title compound **28** (53.7 mg, 74%).

Physical data for **28**. Colorless liquid. Anal. Calcd for $C_{14}H_{22}O_2$ (204.31): C, 75.63; H 9.97. Found: C, 75.17; H, 9.49. IR (film, cm^{-1}): 3081, 3023, 2961, 2874, 1709, 1656, 1626, 1598, 1465, 1427, 1391, 1317, 897. ^{1}H NMR (δ): 5.85 (d, J = 11.9, 1H); 5.80−5.65 (m, 1H); 5.53−5.44 (m, 1H); 5.23 (dd, J_1 = J_2 = 11.6, 1H); 5.10 (s, 1H); 4.98 (s, 1H); 3.85 (dd, J_1 = 15.6, J_2 = 10.7, 1H); 3.34 (dd, J_1 = 16.3, J_2 = 6.3, 1H); 3.20−3.02 (m, 1H); 2.89 (dd, J_1 = 16.3, J_2 = 6.6, 1H); 2.70−2.48 (m, 2H); 2.22 (dd, J_1 = 13.4, J_2 = 10.4, 1H); 1.56 (hept, J = 7.0, 1H); 0.97 (d, J = 3.2, 3H); 0.93 (d, J = 3.2, 3H). ^{13}C NMR (δ): 210.6 (C); 144.4 (C); 133.8 (CH); 130.9 (CH); 128.9 (CH); 124.6 (CH); 115.7 (CH_2); 50.2 (CH_2); 41.2 (CH); 38.4 (CH_2); 36.5 (CH_2); 33.0 (CH); 20.5 (CH_3); 20.4 (CH_3).

(3*Z*,7*E*)-9-Isopropyl-6-methylenecyclodeca-3,7-dienone (29). In a Pyrex vessel with external water cooling, a solution of **28** (260 mg, 1.272 mmol) and diphenyl disulfide (5.6 mg, 26 μmol) in benzene (2.4 mL) was irradiated with a Xenophot 250 W sunlamp for 10 min. The solvent was evaporated under reduced pressure, and the residue was purified by dry-flash chromatography on silver nitrate impregnated silica gel (10% $AgNO_3$ on SiO_2, eluent: petroleum ether:ethyl acetate = 9:1) to give **28** (eluted first, 150 mg), followed by the title compound **29** (100 mg, 38.5%, 91% based on the recovered **28**) as a colorless liquid. In the repeated experiments, the yields varied from 85 to 100% with a ratio of isomers of **29**:**28** = 1.2:1−1:1.5.

Physical data for **29**. Colorless liquid. IR (film, cm^{-1}): 3078, 3023, 2962, 2876, 1709, 1655, 1615, 1448, 1314, 1257, 1118, 1082, 978. ^{1}H NMR (δ): 5.90 (d, J = 16.2, 1H); 5.67 (dd, J_1 = 15.9, J_2 = 10.1, 1H); 5.71−5.45 (m, 2H); 4.97 (d, J = 1.3, 1H); 4.76 (d, J = 1.4, 1H); 3.53 (dd, J_1 = 15.9, J_2 = 10.5, 1H); 3.25−3.14 (m, 1H); 2.80−2.36 (m, 4H); 2.21−2.04 (m, 1H); 1.70−1.53 (m, 1H); 0.93 (d, J = 4.2, 3H); 0.90 (d, J = 4.2, 3H). ^{13}C NMR (δ): 211.7 (C); 144.7 (C); 134.8 (CH); 131.0 (CH); 129.7 (CH); 123.4 (CH); 113.0 (CH_2); 49.8 (CH_2); 47.6 (CH); 43.7 (CH); 35.9 (CH); 32.2 (CH_2); 20.1 (CH_3); 20.0 (CH_3).

Periplanone C (17) (Regioselective Methylenation of 29).[45] To a cold (−20 °C) solution of diisopropylamine (50 mg, 0.492 mmol) in THF (630 μL) was added the solution of *n*-butyllithium in hexane (294 μL of the 1.67 M solution, 0.491 mmol). The solution was stirred for 15 min at that temperature, then cooled to −78 °C, and the solution of compound **29** (91.3 mg, 0.447 mmol) in THF (400 μL) was added. HMPA (319 mg, 1.78 mmol) was added to the solution of the lithium enolate, and the resulting solution was transferred via cannula to a cold (−78 °C) suspension of the Eschenmoser's salt (200 mg, 1.08 mmol) in THF (1 mL). (In order to secure the quantitative transfer of the enolate, the first flask was washed with two 250 μL portions of THF.) The reaction mixture was allowed to reach rt with stirring, when the yellow suspension went into solution. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), and the product was extracted with ethyl acetate (4 × 25 mL). The organic extract was washed with brine, dried over anhydrous $MgSO_4$, filtered off, and concentrated under reduced pressure. The crude residue (430 mg) was dissolved in diethyl ether (3 mL), methyl iodide (1 mL, 2.275 g, 16.28 mmol) was added, and the reaction mixture was stirred at rt for 2 h. The solution of NaOAc (1.2 g) in water (7 mL) was added, and the reaction mixture was vigorously stirred for 1 h. The mixture was diluted with *n*-hexane (80 mL) and water (10 mL), the phases were separated, and the aqueous phase was extracted with *n*-hexane (2 × 10 mL). The combined extract was thoroughly washed with water, dried over anhydrous $MgSO_4$, filtered off, and concentrated under reduced pressure. Purification of the crude organic residue (107 mg) by column chromatography (gradient elution with *n*-hexane:diethyl ether = 95:5→9:1) afforded periplanone C **17** (35.3 mg, 36.5%, 53% based on the recovered **29**) followed by the starting compound **29** (28 mg). (The yield of **17**, determined by ^{1}H NMR of the crude reaction mixture, calculated on the basis of the recovered **29**, was 84%.)

The compound **17** had IR and ^{1}H and ^{13}C NMR spectra identical to those described in the literature.[36,34c]

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Supporting Information Available: Experimental procedures, characterization data, and copies of spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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