Synthesis of Cyclic Bis(trimethysilyl) Enol Ethers and Their [3 + 4] and [3 + 5] Annulation Reactions with Dicarbonyl Electrophiles. Access to Highly Functionalized Tricyclic Ethers Possessing Trans Intrabridgehead Stereochemistry

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The synthesis of cyclic bis(trimethylsilyl) enol ethers from cycloalkanone carboxylates is described. The [3 + 4] and [3 + 5] annulation reactions of these bis(dinucleophilic) synthons with various 1,4- and 1,5-dicarbonyl electrophiles leads to the formation of tricyclic keto ethers with good regio- and stereochemical control. An interesting trans intrabridgehead stereochemistry is observed when using bis(trimethylsilyl) enol ethers derived from nine- to 12-membered ring β-keto esters.

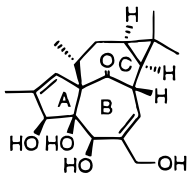
Introduction

The mechanism of action of tumor-promoting substances is of great interest, particularly as it relates to the mechanism of carcinogenesis.[2] Especially useful for the understanding of these processes are ingenol esters (Scheme 1) that can substitute for diacyl glycerol, the endogenous activator of proteins kinase C (PKC).[2b,3] PKC is the phosphorylating enzyme mediating signal transduction for a large class of hormones that activate membrane phosphatidylinositol 4,5-bis(phosphate) turnover.[4] Given the role of PKC in multiple biological processes, an agent selective for inhibition of specific enzymes or the subset of the cascade of responses triggered by PKC would be of great therapeutic value in chronic inflammatory and proliferative disease treatments.[5]

Intensive research has been undertaken to determine how the structurally diverse family of exogenous PKC activators (e.g., bryostatins, teleocidins, aplysiatoxins, phorbols, and ingenol) mimic the action of diacyl glycerol. The recent publication of a crystal structure of the PKCδ zinc finger/phorbol 13-acetate has demonstrated critical interactions in the protein ligand array.[6] These include crucial hydrogen bonds in the hydrophilic region that are common to ingenol and other PKC activators.

Among the different classes of high-affinity ligands for PKC, ingenols are of intense interest because of the very sparse structure/activity data available. The complex and highly oxygenated diterpene ingenol and its analogues

Scheme 1



Ingenol

have not yielded to total synthesis, and several synthetic challenges have thwarted efforts toward its synthesis.[7] Perhaps the most daunting is the construction of the "inside−outside" or trans intrabridgehead stereochemistry of the bicyclo[4.4.1]undecanone ring system that has been the nemesis of several attempted syntheses.[8] Successful approaches to this unusual ring system have been reported by the groups of Winkler,[9] Funk,[10] and Rigby.[11] The importance of this stereochemistry at the critical ring junction is demonstrated by the complete lack of biological activity of the cis epimer synthesized by Paquette.[8a]

Another crucial structural feature of these molecules lies in their hydrophilic regions. Numerous fatty acid ester derivatives at the C3 hydroxyl of ingenol are known to be tumor-promoting species.[4,10]

The Lewis acid-promoted [3 + 4] and [3 + 5] annulation reaction of 1,4- and 1,5-dicarbonyl substrates with bis(trimethylsilyl) enol ethers is among the more versatile methods to access seven- and eight-membered carbocycles (Scheme 2).[12] A unique mechanism, based on neighboring

(1) To whom all correspondence concerning X-ray structures should be addressed.

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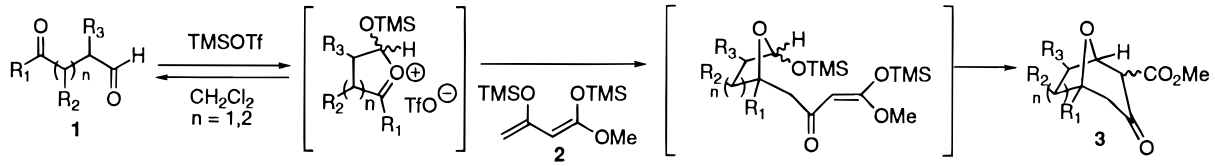
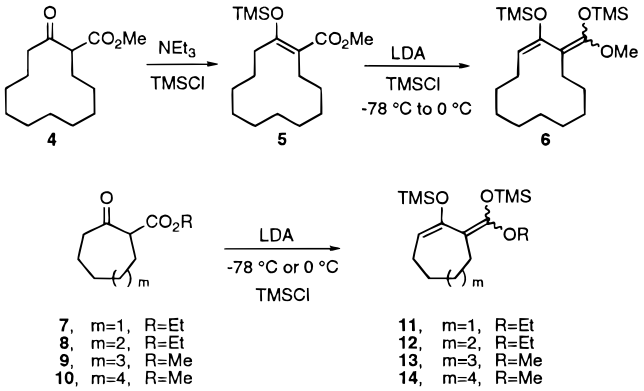
Scheme 2



Scheme 3



group participation and involving an intermediate oxocarbenium ion, permits excellent control over the regio- and stereochemistry of the annulated product. A wide variety of 1,4- and 1,5-dicarbonyl electrophiles have been used as substrates in these annulations, some directed toward the synthesis of natural products such as (+)-dactylol[13] and (±)-furan ether B.[14]

Although the structural diversity accessible by changing the substitution pattern of the dielectrophiles is wide, the possibilities for additional variability can be further expanded by modifying the dinucleophile. Herein we report the first synthesis of cyclic bis(trimethylsilyl) enol ethers starting from cycloalkanone carboxylates and the use of these bis(trimethylsilyl) enol ethers as dinucleophiles in the [3 + 4] and [3 + 5] annulation reaction with a variety of dicarbonyls. As it transpires, the annulation leads to products possessing trans intrabridgehead stereochemistry when nine- to 12-membered ring bis(trimethylsilyl) enol ethers are utilized, affording analogues of the BC ring system of ingenol.

Results and Discussion

Access to a wide variety of tricyclic ethers through the [3 + 4] and [3 + 5] annulation reaction has previously been reported by using cyclic dielectrophiles,[12c] but cyclic dinucleophiles have never been used in such reactions. Furthermore, to the best of our knowledge no cyclic bis(trimethylsilyl) enol ethers derived from cycloalkanone carboxylates have been previously reported in the literature. The seven- to 12-membered ring β-keto esters **4** and **7**−**10** (Scheme 3) were prepared according to literature procedures.[15] Preliminary studies showed that the smaller ring (i.e., seven- and eight-membered) bis(trimethylsilyl) enol ethers would be more difficult to access. The ethyl esters were utilized for the preparation of the bis(trimethylsilyl) enol ethers because of a greater tendency of the methyl esters to undergo C-silylation rather than O-silylation.[16]

Starting with carbomethoxycyclododecanone **4** (Scheme 3), the corresponding bis(trimethylsilyl) enol ether **6** could be accessed using the same procedure as for the acyclic β-keto esters: overnight stirring of **4** with triethylamine and TMSCl in THF afforded, after Kugelrohr distillation, pure monosilyl enol ether **5**. Subsequent treatment with LDA in THF at −78 °C for 1 h followed by trapping of the enolate with TMSCl and warming to room temperature gave bis(trimethylsilyl) enol ether **6** in 88% overall yield as an 85/15 mixture of isomers. The crude product was used without purification in the annulation reactions.

Extension of this high-yielding procedure to the smaller ring sizes (i.e., seven- to 10-membered rings) was problematic. Although the monosilyl enol ethers could be easily accessed in the same way, further treatment with LDA at −78 °C followed by addition of TMSCl led to only a 60% conversion to the bis-silylated products. Performing the same reaction at 0 °C afforded mainly decomposed material. The synthesis of these substrates was finally achieved using two different procedures according to the ring size (Scheme 3). The seven- and eight-membered bis(silyl) enol ethers **11** and **12** were obtained by reaction of the keto esters with 2.5 equiv of LDA at 0 °C for 1.5 h with subsequent addition of 3 equiv of TMSCl. Substrates **13** and **14** were synthesized by performing a double deprotonation at −78 °C followed by addition of TMSCl and warming to 0 °C. In both cases, 90−95% conversion to the desired product was achieved, together with 5−10% of the monosilyl enol ether derivatives. These compounds decomposed extensively after standing overnight at room temperature but could be stored under Ar at −20 °C for several weeks. Because of their instability, these new compounds were characterized only by NMR and high-resolution mass spectrometry. Preparative HPLC, using a reversed-phase C18 column, was the only purification method found to be successful. However, because the use of the purified compounds did not afford better yields in the annulation reactions, the crude products were generally utilized for the synthetic studies.

The 1,4- and 1,5-dicarbonyl substrates **1a**−**h** (Scheme 2, Table 1) used in the annulation reaction were chosen in order to demonstrate the general use of the method and to establish the regio- and stereoselectivities in the reaction. Of special interest were the phenylthio-substituted dielectrophiles **1e**−**g**, which, after annulation,

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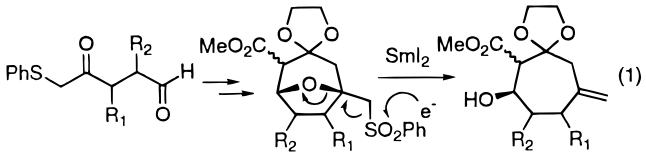
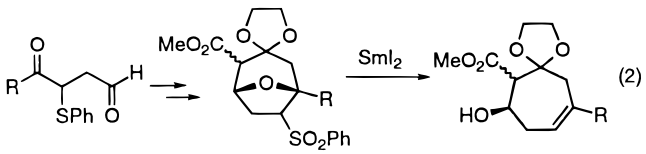
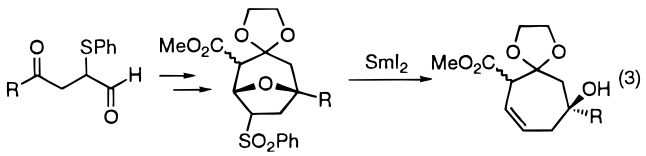
Table 1. Lewis Acid Promoted [3 + 4] and [3 + 5] Annulation Reactions of Cyclic Bis(trimethylsilyl) Enol Ethers with 1,4- and 1,5-Dicarbonyls 1a−h

entry	bis TMS enol ether	substrate	product	*n*	*m*	R_1	R_2	R_3	% isolated yield	ds
1	**6**	**1a**	**15a**	1	6	Pr	H	H	80	
2	**6**	**1b**	**15b**	1	6	Me	H	H	74	
3	**6**	**1c**	**15c**	1	6	Et	Me	H	65	32:1
4	**6**	**1d**	**15d**	1	6	Me	H	Me	71	24:1
5	**6**	**1e**	**15e**	1	6	$PhSCH_2$	H	H	54	
6	**6**	**1f**	**15f**	1	6	Me	PhS	H	51	>200:1
7	**6**	**1g**	**15g**	1	6	Me	H	PhS	60	1.5:1
8	**6**	**1h**	**15h**	2	6	Pr	H	H	66	
9	**14**	**1a**	**15i**	1	4	Pr	H	H	38	
10	**13**	**1a**	**15j**	1	3	Pr	H	H	27	
11	**12**	**1a**	**16a**	1	2	Pr	H	H	35	
12	**12**	**1b**	**16b**	1	2	Me	H	H	28	
13	**11**	**1a**	**16c**	1	1	Pr	H	H	30	

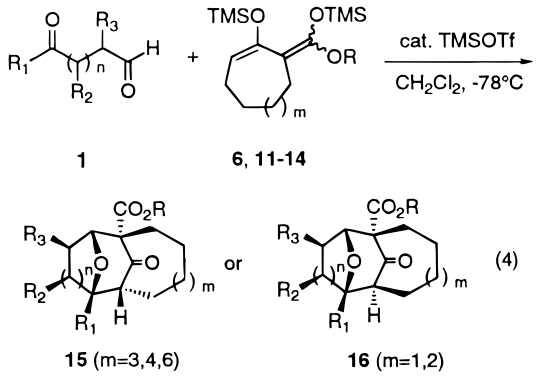
oxidation to the sulfone, and reduction with SmI_2, can lead to ether-cleaved products (eqs 1−3).[12e]



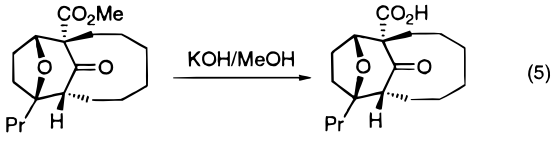


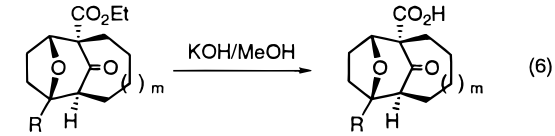


The results of the [3 + 4] and [3 + 5] annulation of the dicarbonyl substrates **1a**−**h** with the cyclic bis-(trimethylsilyl)enol ethers **6** and **11**−**14** (eq 4) are presented in Table 1. Moderate to good yields of the tricyclic ethers were obtained.



The following points are of importance. In all of the [3 + 4] annulations TMSOTf was employed as the catalyst. In the [3 + 5] annulation, $TrSbCl_6$ was used as the Lewis acid, even though only slightly better yields were obtained than when using TMSOTf.[12b] The annulations were totally regioselective, with initial attack occurring at the more hindered ketone carbonyl, implying the involvement of the neighboring group participation mechanism outlined in Scheme 2. Each annulated product existed as a single isomer at the bridgehead position. Most interesting was the stereochemistry at the ketone bridgehead. In the [3 + 4] annulation reaction of **6**, **13** and **14**, as well as in the [3 +5] annulation reaction of **6**, a trans intrabridgehead stereochemistry was observed (compounds **15a**−**j**). In the [3 + 4] annulation of **11** and **12**, a cis stereochemistry was obtained (compounds **16a**−**c**). These stereochemistries have been established by X-ray crystallography, either on the ester (**15b**,**h**,**i**) or on the corresponding acid obtained after saponification (**17j**, **18b**,**c**, eqs 5 and 6).[17]





For annulation products **15** and **16**, the six-membered ring keto ether is in a chairlike conformation with the carboxyl group in a pseudoequatorial orientation, pointing in the same direction as the ketone. Thus, the opposing bridgehead hydrogen is in a pseudoequatorial orientation (cis stereochemistry) for **16a**−**c** and in a pseudoaxial orientation (trans stereochemistry) for **15a**−**j**. Similar trends in stereochemistry have been observed by Noyori.[18] The change in orientation of the bridgehead hydrogen is also reflected in the ^1H NMR signal. In the trans compounds, the proton is in the deshielding cone of the ketone, showing a distinct doublet (it couples only with the cis proton of the neighboring methylene) in the 2.8−3.8 ppm region, with a relatively large coupling constant (10.5−11.0 Hz) owing to the dihedral angle present in the trans compound. In the cis compounds **16** no such distinct low-field signal is present.

Although previous investigations have indicated that these annulations are under kinetic control,[12] it is interesting to note that computational studies on bicyclo-

(17) No isomerisation was detected during the saponification as similar NMR patterns were observed in the esters and the acids.

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[4.4.1]undecane and bicyclo[5.4.1]dodecane indicate that the cis isomer is more stable than the trans by 1−10 kcal/mol. For bicyclotridecane, bicyclotetradecane, and bicycloheptadecane (which can be taken as models for compounds **15a**−**j**), the trans isomer is the most stable.[19] Although no calculations have been made on compounds **15a**−**j**, it is most likely that the trans isomers obtained are the thermodynamically most stable isomers.

The diastereoselectivity was excellent when a stereogenic center existed adjacent to the ketone (entries 3 and 6, Table 1) and highly dependent on the substituent when it was next to the aldehyde (entries 4 and 7, Table 1). The results achieved with the thioether-substituted dicarbonyl substrates are somewhat surprising because the relative magnitudes of diastereoselection for the two regioisomers are reversed from those previously observed with acyclic bis(TMS) enol ether **2** (Scheme 2).[12] The stereochemistry of the major isomers for entries 4 and 7 was determined to be exo by ^{1}H NMR. Molecular models show that the ether bridgehead proton couples only to the exo proton and in the major diastereomers obtained this signal appears as a singlet. For compounds with a substituent next to the alkyl-bridgehead group (**15c** and **15f**) no such NMR study was possible. An X-ray crystal structure was obtained for **15f**, showing the phenylthio substituent to be exo as expected based upon previous examples.[12] Utilizing this information, the same exo stereochemistry was assigned to the methyl substituent in **15c**.

Conclusions

The Lewis acid-promoted [3 + 4] and [3 + 5] annulation reactions of 1,4- and 1,5-dicarbonyl substrates have been extended to cyclic bis(trimethylsilyl) enol ether dinucleophiles. These new compounds were prepared in a one- or two-step sequence from the corresponding cyclic β-keto ester. Regioselectivity and diastereoselectivity are high and predictable based on a cyclic oxocarbenium ion intermediate. The tricyclic keto ethers obtained are amply endowed with functionality, allowing further elaboration of the initial annulation product. Of particular interest are the phenylthio-substituted products that will allow cleavage of the ether bridge. In the case of the annulation of the nine- to 12-membered ring bis(trimethylsilyl) enol ethers, the annulated product possesses an interesting trans intrabridgehead stereochemistry, resembling the ingenol BC ring system. This method thus represents one of the few general methods developed to access this structurally unusual class of molecules.

Experimental Section

Reagents. THF was distilled prior to use from benzophenone ketyl under Ar. Dichloromethane was freshly distilled from CaH_2. TMSOTf was distilled immediately before use, at atmospheric pressure under Ar. TMSCl was distilled and stored over CaH_2. Cyclic keto esters were prepared according to literature procedures. 1,4- and 1,5-dicarbonyl substrates **1a**−**h** were prepared according to reported procedures.[12] Preparative HPLC was realized on a Waters 600E system, using a C18 25 × 100 mm column, with acetonitrile as the mobile phase.

2-(Methoxycarbonyl)-1-(trimethylsiloxy)cyclododec-1-ene (5). TMSCl (2.91 g, 27 mmol) was added to a solution of 1-carbomethoxycyclododecanone (3.87 g, 18 mmol) and triethylamine (2.73 g, 27 mmol) in THF (25 mL), and the mixture was stirred overnight. After concentration, hexane was added, and the suspension was filtered to afford, after concentration and Kugelrohr distillation (ot: 120 °C, 0.3 mmHg), 4.98 g (94%) of the title compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.47−3.53 (m, 1H), 2.45−2.51 (m, 1H), 2.61−2.20 (m, 1H), 1.80−2.20 (m, 1H), 1.57−1.64 (m, 2H), 1.04−1.47 (m, 14H), 0.20 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.99, 165.54, 115.12, 50.63, 33.51, 25.79, 25.72, 25.53, 25.42, 25.10, 24.84, 24.73, 24.09, 0.70; IR (neat) 1709.6, 1604.9, 935.6, 846.3 cm^{-1}; HRMS calcd for $C_{17}H_{32}O_3Si$ 312.2121, found 312.2109; LRMS (EI) *m*/*z* 312 (70), 297 (100).

3-[(Methoxy)(trimethylsiloxy)methylidene]-2-(trimethylsiloxy)cyclododec-1-ene (6). To a solution of LDA (5.5 mmol) in THF (7.5 mL) at −78 °C was added a solution of **5** (1.56 g, 5 mmol) in THF (2.5 mL). After the mixture was stirred 1 h at −78 °C, TMSCl (0.65 g, 6 mmol) was added, and the resulting mixture was warmed to 0 °C and stirred for 3 h. After concentration, hexane was added and the suspension was filtered to afford 1.80 g (94%) of the title compound as a mixture of isomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (t, J = 7.0 Hz, 1H), 3.49 (s, 3H), 2.04−2.09 (m, 4H), 1.20−1.41 (m, 14H), 0.19 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.17, 146.10, 113.80, 101.28, 56.42, 26.854, 26.61, 26.27, 26.16, 25.81, 24.74, 24.34, 0.37, 0.28; IR (neat) 1661.3, 974.4, 625.2, 908.7, 845.0 cm^{-1}; HRMS calcd for $C_{20}H_{40}O_3Si_2$ 384.2616, found 384.2495; LRMS (EI) *m*/*z* 384 (70), 369 (50), 353 (100), 73 (100).

General Procedure for the Synthesis of Seven- and Eight-Membered Ring Bis(trimethylsilyl) Enol Ethers. To a solution of LDA (2.2 equiv) in THF (1 mL/1.1 mmol) at 0 °C was added dropwise the keto ester (1 equiv) in THF (1 mL/1 mmol). After the mixture was stirred for 1.5 h at 0 °C, TMSCl (3 equiv) was added in one portion, and the mixture was stirred for an additional 1 h. After evaporation of the solvents, hexane was added. The resulting suspension was filtered and concentrated to afford the bis(trimethylsilyl) enol ether in 90−95% crude yield together with 5−10% of the monosilyl compound. Purification was realized using preparative HPLC.

3-[(Ethoxy)(trimethylsiloxy)methylidene]-2-(trimethylsiloxy)cyclohept-1-ene (11). Following the general procedure, 2-carbethoxycycloheptanone afforded the title compound in 90% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90 (t, J = 6.5 Hz, 1H), 3.81 (q, J = 7.0 Hz, 2H), 2.14−2.17 (m, 2H), 1.94−1.97 (m, 2H), 1.55−1.60 (m, 2H), 1.47−1.51 (m, 2H), 1.21 (t, J = 7.0 Hz, 3H), 0.20 (s, 9H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.23, 150.68, 109.44, 98.78, 63.55, 30.38, 27.56, 26.86, 25.65, 15.07, 0.33, 0.29; IR (neat) 3330.5, 3076.4, 1645.1, 1060.4 cm^{-1}; HRMS calcd for $C_{16}H_{32}O_3Si_2$ 328.1890, found 328.1888; LRMS (EI) *m*/*z* 328 (100), 199 (35), 283 (35), 73 (100).

3-[(Ethoxy)(trimethylsiloxy)methylidene]-2-(trimethylsiloxy)cyclooct-1-ene (12). Following the general procedure, 2-carbethoxycyclooctanone afforded the title compound in 95% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.73 (t, J = 7.5 Hz, 1H), 3.81 (q, J = 7.0 Hz, 2H), 2.16−2.18 (m, 2H), 1.92−1.95 (m, 2H), 1.42−1.50 (m, 6H), 1.23 (t, J = 7.0 Hz, 3H), 0.18 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.65, 149.91, 107.70, 99.35, 64.85, 30.22, 30.02, 28.32, 27.34, 26.39, 15.75, 1.31, 0.97; HRMS calcd for $C_{17}H_{34}O_3Si_2$ 342.2047, found 342.2042; LRMS (EI) *m*/*z* 342 (100), 317 (40), 313 (70), 73 (100).

General Procedure for the Synthesis of Nine- and 10-Membered Ring Bis(trimethylsilyl) Enol Ethers. To a solution of LDA (2.5 equiv) in THF (1 mL/1.25 mmol) at −78 °C was added dropwise the keto ester (1 equiv) in THF (1 mL/1 mmol). After the mixture was stirred for 2 h at −78 °C, TMSCl (6 equiv) was added in one portion, and the mixture was warmed to 0 °C and stirred for an additional 2 h. After evaporation of the solvents, hexane was added. The resulting suspension was filtered and concentrated to afford the bis(trimethylsilyl) enol ether in crude quantitative yield. Purification was realized using preparative HPLC.

3-[(Methoxy)(trimethylsiloxy)methylidene]-2-(trimethylsiloxy)cyclonon-1-ene (13). Following the general procedure, 2-carbomethoxycyclononanone afforded the title com-

(19) For a review on inside−outside bridghead systems, see: Alder, R. W.; East, S. P. *Chem. Rev.* **1996**, *96*, 2097.

pound in 97% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 (t, J = 8.5 Hz, 1H), 3.51 (s, 3H), 2.07 (t, J = 6.0 Hz, 2H), 1.99−2.07 (m, 2H), 1.51−1.57 (m, 2H), 1.21−1.52 (m, 6H), 0.19 (s, 9H), 0.16 (s, 9H); IR (neat) 1679.2, 1643.0, 905.3, 844.8 cm^{-1}; HRMS calcd for $C_{17}H_{34}O_3Si_2$ 342.2047, found 342.2034; LRMS (EI) *m/z* 342 (20), 270 (20), 73 (100).

3-[(Methoxy)(trimethylsiloxy)methylidene]-2-(trimethylsiloxy)cyclodec-1-ene (14). Following the general procedure, 2-carbomethoxycyclodecanone afforded the title compound in 96% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (t, J = 8.0 Hz, 1H), 3.49 (s, 3H), 2.08−2.12 (m, 2H), 1.95−2.05 (m, 2H), 1.22−1.48 (m, 10H), 0.18 (s, 9H), 0.1 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.97, 145.50, 115.01, 101.64, 56.24, 28.19, 26.96, 25.64, 25.35, 24.59, 24.55, 24.49, 0.49, 0.32; IR (neat) 1658.4, 1598.5, 843.9 cm^{-1}; HRMS calcd for $C_{18}H_{36}O_3Si_2$ 356.2203, found 356.2186; LRMS (EI) *m/z* 356 (100), 341 (70), 325 (70), 73 (100).

General Procedure for the Annulation of 1,4-Dicarbonyl Substrates. A solution of TMSOTf (0.20 mmol) in CH_2Cl_2 (2 mL) precooled to −78 °C was added dropwise to a solution of the bis(trimethylsilyl) enol ether (0.65 mmol) and of the dicarbonyl substrate (0.50 mmol) in CH_2Cl_2 (11 mL) at −78 °C over 2 min. The reaction mixture was stirred for 2−8 h at −78 °C and then was quenched by addition of pH = 7 phosphate buffer. After the mixture was warmed to room temperature, the layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated. Purification by flash chromatography over silica gel (hexane/ethyl acetate 20:1) provided the annulated product.

(1*R,11*S**,12*R**,15*S**)-1-(Methoxycarbonyl)-12-propyl-17-oxatricyclo[9.4.1.1^{12,15}]heptadecan-16-one (15a).** Following the general procedure, **6** was annulated with **1a** for 3 h to give, after flash chromatography, 140 mg (80%) of the title compound: mp (hexane) 95 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (d, J = 7.0 Hz, 1H), 3.71 (s, 3H), 3.06 (d, J = 11.0 Hz, 1H), 2.36 (ddd, J = 2.0, 10.0, 15.0 Hz, 1H), 1.98−2.08 (m, 1H), 1.68−1.96 (m, 4H), 1.04−1.62 (m, 19H), 0.96 (t, J = 7.0 Hz, 3H), 0.91 (t, J = 12.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.30, 170.60, 89.84, 81.50, 67.19, 54.01, 51.59, 39.41, 32.35, 31.50, 30.04, 29.02, 26.29, 25.80, 23.17, 22.81, 22.07, 21.76, 20.80, 16.70, 14.42; IR (neat) 1755.9, 1716.3 cm^{-1}; HRMS calcd for $C_{21}H_{34}O_4$ 350.2457, found 350.2469; LRMS (EI) *m/z* 350 (65), 240 (100), 306 (50), 279 (40). Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.77. Found: C, 71.62; H, 9.76.

(1*R,11*S**,12*R**,15*S**)-1-(Methoxycarbonyl)-12-methyl-17-oxatricyclo[9.4.1.1^{12,15}]heptadecan-16-one (15b).** Following the general procedure, **6** was annulated with **1b** for 3 h to give, after flash chromatography, 120 mg (74%) of the title compound: mp (hexane) 75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.46 (d, J = 7.0 Hz, 1H), 3.71 (s, 3H), 2.98 (d, J = 11.0 Hz, 1H), 2.45 (ddd, J = 2.0, 10.0, 14.5 Hz, 1H), 2.08−2.15 (m, 1H), 1.86−1.93 (m, 3H), 1.04−1.69 (m, 19H), 0.91 (t, J = 12.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.74, 170.68, 87.91, 81.48, 67.22, 56.14, 51.66, 32.33, 31.18, 29.29, 26.20, 25.63, 24.70, 23.01, 22.72, 22.22, 22.18, 21.83, 20.96; IR (neat) 1572.2, 1734.0, 1718.0, 1712.8 cm^{-1}; HRMS calcd for $C_{19}H_{30}O_4$ 322.2144, found 322.2132; LRMS (EI) *m/z* 322 (100), 291 (50), 278 (60), 240 (100), 219 (90). Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.77. Found: C 70.53; H, 9.53.

(1*R,11*S**,12*R**,13*R**,15*S**)-12-Ethyl-1-(methoxycarbonyl)-13-methyl-17-oxatricyclo[9.4.1.1^{12,15}]heptadecan-16-one (15c).** Following the general procedure, **6** was annulated with **1c** for 2 h to give, after flash chromatography and Kugelrohr distillation (ot 140−145 °C, 0.4 mmHg), 113 mg (65%) of the title compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.36 (d, J = 7.0 Hz, 1H), 3.69 (s, 3H), 3.10 (d, J = 11.0 Hz, 1H), 2.31 (ddd, J = 1.5, 10.0, 14.5 Hz, 1H), 2.24 (dd, J = 9.0, 13.5 Hz, 1H), 1.85−1.95 (m, 2H), 1.72−1.81 (m, 1H), 1.62−1.72 (m, 1H), 1.15−1.60 (m, 16H), 1.10 (t, J = 7.5 Hz, 3H), 0.84 (t, J = 12.5 Hz, 1H), 0.80 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.07, 170.65, 91.23, 79.90, 67.09, 52.78, 51.64, 39.51, 35.05, 32.05, 26.48, 25.96, 25.08, 23.36, 22.97, 22.39, 22.02, 21.79, 20.85, 17.99, 8.41; IR (neat) 1754.8, 1720.1, 1712.3 cm^{-1}; HRMS calcd for $C_{21}H_{34}O_4$ 350.2407, found 350.2467; LRMS (EI) *m/z* 350 (15), 319 (20), 240 (100), 222 (100), 111 (100). Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.03; H, 9.85.

(1*R,11*S**,12*R**,14*S**,15*S**)-1-(Methoxycarbonyl)-12,14-dimethyl-17-oxatricyclo[9.4.1.1^{12,15}]heptadecan-16-one (15d).** Following the general procedure, **6** was annulated with **1d** for 2 h to give, after flash chromatography and Kugelrohr distillation (ot 100−105 °C, 0.15 mmHg), 119 mg (71%) of the title compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99 (s, 1H), 3.69 (s, 3H), 2.90 (d, J = 10.5 Hz, 1H), 2.41 (ddd, J = 2.5, 10.5, 15.0 Hz, 1H), 2.13−2.20 (m, 1H), 1.75−1.98 (m, 3H), 1.04−1.60 (m, 17H), 1.03 (d, J = 7.0 Hz, 3H), 0.90 (ddd, J = 1.5, 4.5, 13 Hz, 1H), 0.86 (t, J = 12.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.43, 171.57, 89.54, 88.78, 67.77, 56.76, 52.30, 41.52, 38.31, 33.02, 26.95, 26.31, 25.92, 23.83, 23.50, 23.22, 22.99, 22.83, 22.58, 21.82; IR (neat) 1754.6, 1715.9 cm^{-1}; HRMS calcd for $C_{20}H_{32}O_4$ 336.2301, found 336.2307; LRMS (EI) *m/z* 336 (15), 240 (100), 305 (25), 293 (30), 222 (75).

(1*R,11*R**,12*S**,15*S**)-1-(Methoxycarbonyl)-12-[(phenylthio)methy]-17-oxatricyclo[9.4.1.1^{12,15}]heptadecan-16-one (15e).** Following the general procedure, **6** was annulated with **1e** for 4 h to give, after flash chromatography, 116 mg (54%) of the title compound: mp (hexane/CH_2Cl_2) 104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.42 (m, 2H), 7.24−7.28 (m, 2H), 7.16−7.20 (m, 1H), 4.50 (d, J = 7.0 Hz, 1H), 3.71 (s, 3H), 3.40 (d, J = 11.0 Hz, 1H), 3.28 (dd, J = 13.0, 19.0 Hz, 2H), 2.41 (ddd, J = 1.5, 10.5, 15.0 Hz, 1H), 2.09−2.19 (m, 1H), 1.82−2.00 (m, 3H), 1.66−1.73 (m, 1H), 1.54−1.64 (m, 2H), 1.06−1.52 (m, 13H), 0.90 (t, J = 12.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.79, 170.44, 136.63, 130.01, 128.89, 126.38, 89.06, 81.71, 67.28, 53.52, 51.74, 42.23, 32.27, 30.25, 29.18, 26.36, 25.81, 23.08, 22.87, 22.50, 22.23, 21.81, 20.84; IR (neat) 1753.7, 1736.2, 1720.2, 1715.4, 738.7, 690.8, 662.4 cm^{-1}; HRMS calcd for $C_{25}H_{34}O_4S$ 430.2178, found 430.2157; LRMS (EI) *m/z* 430 (100), 321 (70), 289 (70), 85 (100).

(1*R,11*S**,12*S**,13*R**,15*S**)-1-(Methoxycarbonyl)-12-methyl-13-(phenylthio)-17-oxatricyclo[9.4.1.1^{12,15}]-heptadecan-16-one (15f).** Following the general procedure, **6** was annulated with **1f** for 4 h to give, after flash chromatography, 110 mg (51%) of the title compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15−7.30 (m, 5H), 4.48 (d, J = 7.5 Hz, 1H), 3.71 (s, 3H), 3.46 (dd, J = 5.0, 8.5 Hz, 1H), 3.01 (d, J = 10.0 Hz, 1H), 2.61 (dd, J = 9.0, 15.0 Hz, 1H), 2.42 (dd, J = 10.5, 14.5 Hz, 1H), 2.14−2.19 (m, 1H), 1.87−1.93 (m, 2H), 1.01−1.70 (m, 17H), 0.88 (t, J = 12.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.42, 170.36, 135.71, 130.30, 129.03, 126.65, 90.45, 80.00, 66.89, 57.14, 51.81, 48.45, 39.70, 32.09, 26.30, 25.69, 23.03, 22.82, 22.23, 22.08, 22.00, 21.83, 21.07; IR (neat) 1725.4, 1715.4, 736.5, 691.5 cm^{-1}; HRMS calcd for $C_{25}H_{34}O_4S$ 430.2178, found 430.2173; LRMS (EI) *m/z* 430 (100), 240 (60), 209 (100), 98 (100). Anal. Calcd for $C_{25}H_{34}O_4S$: C, 69.73; H, 7.95. Found: C, 69.47; H, 8.15.

1-(Methoxycarbonyl)-12-methyl-14-(phenylthio)-17-oxatricyclo[9.4.1.1^{12,15}]heptadecan-16-one (15g). Following the general procedure, **6** was annulated with **1g** for 4 h to give, after flash chromatography, the following two diastereomers. **(1*R**,11*S**,12*R**,14*S**,15*R**)-15g:** 90 mg (42%) of the title compound; mp 88 °C (hexane); ^{1}H NMR (500 MHz, C_6D_6) δ 7.36−7.38 (m, 2H), 6.88−6.98 (m, 3H), 4.52 (s, 1H), 4.28 (dd, J = 4.1, 8.5 Hz, 1H), 3.17 (s, 3H), 2.94 (d, J = 10.2 Hz, 1H), 2.37 (ddd, J = 1.8, 9.7, 14.5 Hz, 1H), 2.11 (dd, J = 8.8, 14.0 Hz, 1H), 1.85−1.97 (m, 1H), 1.58−1.80 (m, 2H), 0.89−1.42 (m, 14H), 1.21, (s, 3H), 0.67 (t, J = 12.5 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 204.60, 169.74, 136.27, 132.78, 129.51, 127.60, 88.62, 88.22, 68.08, 56.47, 51.67, 49.73, 41.05, 32.57, 27.00, 26.52, 25.35, 23.54, 23.51, 22.90, 22.83, 22.59, 21.47; IR (neat) 1751.5, 1723.8, 739.8, 692.6 cm^{-1}; HRMS calcd for $C_{25}H_{34}O_4S$ 430.2178, found 430.2163; LRMS (EI) *m/z* 430 (100), 321 (20), 289 (30), 261 (35). Anal. Calcd for $C_{25}H_{34}O_4S$: C, 69.73; H, 7.95. Found: C, 69.79; H, 8.12.

(1*R,11*S**,12*R**,14*R**,15*R**)-15g:** 60 mg, (18%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22−7.29 (m, 4H), 7.14−7.17 (m, 1H), 5.01 (d, J = 6.5 Hz, 1H), 4.00 (ddd, J = 6.5, 8.0, 12.0 Hz, 1H), 3.25 (s, 3H), 3.16 (d, J = 11.5 Hz, 1H), 2.60 (ddd, J = 2.5, 10.5, 13.0 Hz, 1H), 2.11 (ddd, J = 1.5, 12.0, 14.0 Hz, 1H), 1.87−

1.98 (m, 2H), 1.64 (dd, J = 8.0, 13.5 Hz, 1H), 1.47−1.57 (m, 2H), 1.47 (s, 3H), 1.10−1.42 (m, 12H), 0.95 (t, J = 12.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.37, 168.78, 137.22, 128.69, 127.23, 125.43, 86.31, 84.07, 62.04, 56.04, 50.95, 46.99, 39.11, 34.86, 25.57, 25.44, 24.66, 22.75, 22.42, 22.29, 22.04, 21.64, 20.10; HRMS calcd for $C_{25}H_{34}O_4S$ 430.2178, found 430.2158; LRMS (EI) *m/z* 430 (100), 321 (20), 289 (30), 261 (35).

(1*R,9*R**,10*R**,13*S**)-1-(Methoxycarbonyl)-10-propyl-15-oxatricyclo[7.4.1.1^{10,13}]pentadecan-14-one (15i).** Following the general procedure, **14** was annulated with **1a** to give, after flash chromatography and Kugelrohr distillation (ot 120−125 °C, 0.4 mmHg), 61 mg (38%) of the title compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.54 (d, J = 7.0 Hz, 1H), 3.81 (dd, J = 3.0, 12.5 Hz, 1H), 3.74 (s, 3H), 2.94 (ddd, J = 4.0, 13.5, 15.5 Hz, 1H), 1.98−2.08 (m, 1H), 1.04−1.92 (m, 20H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.96, 170.93, 92.31, 82.34, 67.29, 53.97, 51.64, 38.90, 31.21, 29.72, 29.58, 26.81, 26.10, 24.42, 23.26, 20.86, 20.09, 17.04, 14.47; IR (neat) 1750.5, 1726.0, 1707.6; HRMS calcd for $C_{19}H_{30}O_4$ 322.2144, found 322.2138; LRMS (EI) *m/z* 322 (20), 291 (30), 212 (100), 71 (90), 43 (100). Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.75; H, 9.53.

(1*R,8*R**,9*R**,12S*R**)-1-(Methoxycarbonyl)-9-propyl-14-oxatricyclo[6.4.1.1^{9,12}]tetradecan-13-one (15j).** Following the general procedure, **13** was annulated with **1a** to give, after flash chromatography and Kugelrohr distillation (ot 110−120 °C, 0.4 mmHg), 42 mg (27%) of the title compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.47 (d, J = 7.5 Hz, 1H), 3.70 (s, 3H), 3.43 (d, J = 10.5 Hz, 1H), 2.57 (ddd, J = 2.0, 11.0, 15.0 Hz, 1H), 1.06−2.16 (m, 18H), 0.93 (t, J = 7.0 Hz, 3H), 0.81 (t, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.40, 171.71, 91.89, 81.01, 66.96, 55.87, 51.74, 39.45, 35.81, 32.94, 30.67, 30.20, 29.48, 26.52, 26.37, 19.51, 17.13, 14.43; IR (neat) 1749.7, 1727.3; HRMS calcd for $C_{18}H_{28}O_4$ 308.1988, found 308.1984; LRMS (EI) *m/z* 308(30), 277 (50), 211 (100), 71 (80), 43 (100).

(1*R,7*R**,8*R**,11S*R**)-1-(Ethoxycarbonyl)-8-propyl-13-oxatricyclo[5.4.1.1^{8,11}]tridecan-12-one (16a).** Following the general procedure, **12** was annulated with **1a** for 8 h to give, after flash chromatography, 54 mg (35%) of the title compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (d, J = 7.0 Hz, 1H), 4.15 (dq, J = 7.0, 3.5 Hz, 2H), 2.48 (ddd, J = 15.0, 9.0, 1.5 Hz, 1H), 2.32 (dd, J = 10.5, 9.0 Hz, 1H), 2.16−2.25 (m, 1H), 2.08−2.15 (m, 1H), 1.40−2.06 (m, 12H), 1.24 (t, J = 7.0 Hz, 3H), 1.16−1.24 (m, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.37, 170.83, 86.89, 80.82, 65.32, 60.82, 59.37, 37.60, 33.40, 30.53, 28.44, 28.10, 24.08, 23.93, 17.36, 16.63, 14.06; IR (neat) 1725.2, 1703.2 cm^{-1}; HRMS calcd for $C_{18}H_{28}O_4$ 308.1988, found 308.1978; LRMS (EI) *m/z* 308 (100), 263 (100), 237 (90), 206 (40). Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.71; H, 9.34.

(1*R,7*R**,8*R**,11*S**)-1-(Ethoxycarbonyl)-8-methyl-13-oxatricyclo[5.4.1.1^{8,11}]tridecan-12-one (16b).** Following the general procedure, **12** was annulated with **1b** for 8 h to give, after flash chromatography, 39 mg (28%) of the title compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (d, J = 7.0 Hz, 1H), 4.16 (ddq, J = 0.5, 5.0, 7.5 Hz, 2H), 2.50 (ddd, J = 2.0, 9.0, 15.0 Hz, 1H), 2.29 (dd, J = 9.0, 11.0 Hz, 1H), 2.02−2.26 (m, 4H), 1.88−1.94 (m, 1H), 1.48−1.86 (m, 6H), 1.35 (s, 3H), 1.29 (dt, J = 0.5, 7.0 Hz, 3H), 1.18−1.27 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.33, 170.83, 84.42, 81.00, 64.96, 61.35, 60.82, 36.03, 30.52, 29.06, 28.33, 24.03, 23.93, 22.42, 14.06; HRMS calcd for $C_{16}H_{24}O_4$ 280.1675, found 280.1682; LRMS (EI) *m/z* 280 (60), 262 (20), 235 (100), 43 (100).

(1*R,2*S**,5*R**,6*R**)-1-(Ethoxycarbonyl)-5-propyl-12-oxatricyclo[4.4.1.1^{2,5}]dodecan-11-one (16c).** Following the general procedure, **11** was annulated with **1a** for 8 h to give, after flash chromatography and Kugelrohr distillation (ot 100−105 °C, 0.6 mmHg), 45 mg (30%) of the title compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.36 (dd, J = 1.5, 7.0 Hz, 1H), 4.18 (dq, J = 7.0, 3.5 Hz, 2H), 2.48 (dd, J = 3.5, 5.5 Hz, 1H), 2.44 (dd, J = 3.5, 5.0 Hz, 0.5H), 2.21 (dd, J = 3.5, 5.5 Hz, 0.5H), 1.62−2.12 (m, 10H), 1.47−1.61 (m, 1H), 1.20−1.39 (m, 4H), 1.22 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.92, 171.99, 85.46, 81.51, 66.00, 60.92, 58.82, 38.02, 35.52, 33.40, 27.72, 27.42, 27.14, 25.46, 17.55, 14.68, 14.10; IR (neat) 1725.5, 1708.6 cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.23; H, 8.98.

(1*R,11*S**,12*R**,16*S**)-1-(Methoxycarbonyl)-12-propyl-18-oxatricyclo[9.5.1.1^{12,16}]octadecan-17-one (15h).** A 0.007 M solution of $TrSbCl_6$ (6.5 mol %) in CH_2Cl_2 was added dropwise over 5 min to a 0.1 M solution of **1h** (1 equiv) in CH_2Cl_2 at −78 °C. After the solution was stirred for 2 min, a −78 °C precooled 0.1 M solution of **6** (1.2 equiv) in CH_2Cl_2 was added dropwise over 5 min. After being stirred at −78 °C for 3 h, the mixture was warmed to room temperature and concentrated. The residue was subjected to flash chromatography to provide the annulated product in 66% yield: mp (hexane) 83−84 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 4.10 (d, J = 5.0 Hz, 1H), 3.36 (s, 3H), 2.86 (d, J = 10.5 Hz, 1H), 2.30−2.34 (m, 2H), 0.93−1.99 (m, 25H), 0.91 (t, J = 7.0 Hz, 3H), 0.75 (dt, J = 3.0, 13.0 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.95, 170.48, 80.81, 78.41, 65.41, 51.63, 51.25, 44.20, 34.92, 31.30, 28.45, 27.18, 27.02, 24.21, 23.50, 23.10, 22.92, 22.07, 19.75, 17.25, 16.55, 15.14; IR (neat) 1753.7, 1736.0, 1723.7, 1708.3 cm^{-1}; HRMS calcd for $C_{22}H_{36}O_4$ 364.2614, found 364.2609; LRMS (EI) *m/z* 364 (100), 332 (20), 305 (30), 261 (50), 125 (60), 71 (90).

General Procedure for the Saponification of Annulated Esters. The annulated ester (0.2 mmol) was heated at reflux for 1.5 h in 0.5 mL of a 1 N solution of KOH in methanol. The mixture was concentrated, dissolved in water (2 mL), washed with AcOEt, acidified with 1 N HCl, extracted with AcOEt, and dried over magnesium sulfate. After concentration, the acid was purified by flash chromatography over SiO_2 (hexane/AcOEt 20:1).

(1*R,8*R**,9*R**,12*S**)-9-Propyl-13-oxo-14-oxatricyclo-[6.4.1.1^{9,12}]tetradecanecarboxylic Acid (17j).** Following the general procedure, **15j** was saponified to give, after flash chromatography, 40 mg (68%) of the title compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.62 (d, J = 7.0 Hz, 1H), 3.53 (d, J = 11.0 Hz, 1H), 2.48−2.56 (m, 2H), 1.18−2.24 (m, 15H), 0.98 (t, J = 7.0 Hz, 3H), 0.96−1.20 (m, 2H), 0.81−0.91 (m, 1H), −0.30 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.71, 172.72, 92.42, 82.38, 65.19, 57.71, 39.41, 38.22, 33.26, 30.53, 30.43, 29.86, 26.69, 26.53, 19.19, 17.04, 14.37.

(1*R,7*R**,8*R**,11*S**)-8-Methyl-12-oxo-13-oxatricyclo-[5.4.1.1^{8,11}]tridecanecarboxylic Acid (18b).** Following the general procedure, **16b** was saponified to give, after flash chromatography, 43 mg (86%) of the title compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (d, J = 7.0 Hz, 1H), 2.58 (dd, J = 5.5, 15.5 Hz, 1H), 2.40−2.45 (m, 2H), 2.13−2.26 (m, 2H), 1.93−2.00 (m, 1H), 1.71−1.91 (m, 5H), 1.57−1.64 (m, 1H), 1.40 (s, 3H), 1.03−1.18 (m, 3H), −0.20 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.37, 173.23, 84.61, 81.03, 62.77, 61.10, 35.99, 35.76, 30.92, 29.00, 28.88, 23.56, 23.39, 22.13.

(1*R,2*S**,5*R**,6*R**)-5-Propyl-11-oxo-12-oxatricyclo-[4.4.1.1^{2,5}]dodecanecarboxylic Acid (18c).** Following the general procedure, **16c** was saponified to give, after flash chromatography, 36 mg (65%) of the title compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.0 (brs, 1H), 4.73 (d, J = 7.0 Hz, 1H), 2.62 (dd, J = 3.0, 6.5 Hz, 1H), 2.12−2.23 (m, 2H), 1.77−2.04 (m, 6H), 1.52−1.67 (m, 4H), 1.38−1.46 (m, 1H), 1.18−1.28, (m, 3H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 217.53, 172.51, 85.74, 81.88, 62.08, 58.10, 37.97, 35.93, 34.81, 28.96, 27.28, 26.78, 24.96, 17.47, 14.63.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds for which no elemental analysis was obtained; X-ray structural information. This material is available free of charge via the Internet at http://pubs.acs.org.

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