Studies Towards the Synthesis of Functionalized Medium-Sized Carbocyclic and Fused Bicyclic Systems by Alkoxy Radical Fragmentation (ARF)

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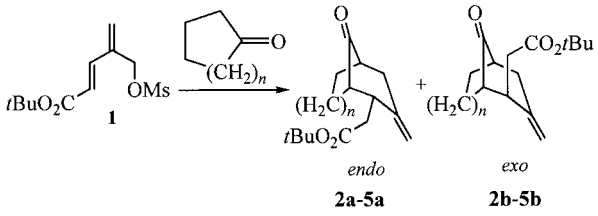
The stereoselective construction of polyfunctionalized medium-sized carbocyclic and fused bicyclic systems from substituted bicyclo[3.*n*.1]alkanones has been studied; the strategy employed involved Suarez's alkoxy radical fragmentation reaction (ARF) as the key step. The scope of the reaction was examined and this methodology was found to be especially useful for stereo- and regioselective construction of eight-membered carbocycles including bicyclo[6.4.0]dodecane systems, a framework that is present in a variety of biologically active natural products. This reaction was also used successfully in the synthesis of seven-membered carbocycles but with low selectivity. It was found that the presence of a hemiketal functionality in the molecule is essential for the ARF reaction to occur; hence nine- and ten-membered ring analogs could not be attained since the precursor bicyclic ketones do not form the required hemiketals. This is borne out by MM calculations. Finally, a diquinane was also synthesized.

Introduction

Polyfunctionalized medium-sized carbocyclic rings, in particular seven- and eight-membered systems, have been found to be an integral part of terpenes and a variety of other natural products, for example, ingenol, taxol, dumortenol and kalmanol, and are thus of immense synthetic interest worldwide.[1,2] Despite the unfavourable enthalpy and entropy factors, as well as transannular interactions, that pose a serious restriction to the classical methods of ring formation and annulation, the last two decades have witnessed an upsurge in research related to the construction of such ring systems. In particular, the emergence of paclitaxel[3] as an anticancer drug has encouraged synthetic chemists to develop newer methodologies for the stereo-, regio- and enantioselective construction of medium-sized carbocycles, in particular cyclooctanes. Some of the strategies that have already been developed include cycloaddition, annulation, sigmatropic cyclization, radical-mediated ring expansion and fragmentation.[1,2] Of these, the radical-mediated ring cyclization/expansion reactions often enjoy unique advantages of being mild, highly reactive, selective and functional group tolerant.[1b,4] The use of free radicals in the synthesis of medium-sized carbocyclic rings has been reviewed extensively by Yet[1b] and Mehta and Singh.[1c] Recently, Cha and co-workers reported that β-scission of alkoxy radicals generated from suitably substituted ketones provides a very useful route to the synthesis of medium-sized carbocyclic rings.[2b,2i,5] Suginome et al. have synthesized many natural products using strategies that involved β-scission of alkoxy radicals as the key step.[6] The synthesis of medium-sized carbocycles by radical or ionic fragmentation of bicyclic compounds has been widely reported in the literature.[7] We previously reported a facile construction of functionalized bicyclo[3.*n*.1]alkanones from a newly designed double-acceptor molecule, namely pentadienoic ester **1** (Scheme 1, Table 1), which has scope for further elaboration.[8] We were interested in demonstrating the accessibility of polyfunctionalized medium-sized rings



Scheme 1. Synthesis of bicyclic ketones from pentadienoic ester **1**.

Table 1. Synthesis of bicyclic ketones **2**–**5**.

n	*endo*	*exo*	Ratio *endo*/*exo*
1	**2a**	**2b**	86:14
2	**3a**	**3b**	100:0
3	**4a**	**4b**	60:40
4	**5a**	**5b**	60:40

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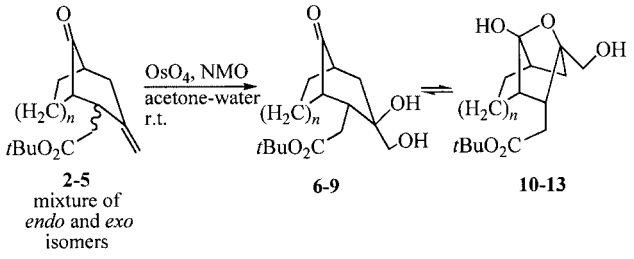
starting from simple cyclic ketones, hence we developed a facile route for the diastereoselective construction of seven- and eight-membered carbocyclic rings from bicyclic ketones, for example, **2**, by radical-mediated ring excision of the keto bridge.[9] We report here a more detailed account of the scope of these reactions.

Results and Discussion

Our envisaged route towards the synthesis of functionalized medium-sized carbocyclic rings involved the cleavage of the carbonyl–C bond in compounds **2**–**5**, hence some structural manipulation of these bicyclic ketones was required. This was accomplished by subjecting the *exo*-methylene group in ketones **2**–**5** (in most cases a mixture of *endo* and *exo* isomers) to a dihydroxylation reaction.[10] Upon treatment with a catalytic amount of OsO_4 in the presence of *N*-methylmorpholine *N*-oxide (NMO), *endo*-substituted bicyclic ketones **2a**–**5a** underwent smooth *exo* dihydroxylation to afford diols **6**–**9** in reasonable yields (Scheme 2, Table 2). The reason for the prevalence of *exo* dihydroxylation can be attributed to the fact that the *endo* face of these bicyclic ketones is sterically hindered, and thus the dihydroxylation occurs exclusively on the convex *exo* side. Interestingly, during the dihydroxylation reaction, the *exo* isomers **2b**, **4b** and **5b** remained intact and could be easily separated from the diol. The size of the ring of the bicyclic ketone had a significant effect on the structures of the diols **6**–**9**; while the keto diols **6** and **7**, obtained from bicyclic ketones **2a** and **3a**, were isolable only in their hemiketal form **10** and **11**, respectively, the diols derived from ketones **4a** and **5a** exist in the dihydroxy form **8** and **9**. This was evidenced by the absence of a ketone carbon signal in the ^{13}C NMR spectra of **6** and **7** as well as by the absence of the ketone C=O stretching frequency in their IR spectra, and by the presence of such signals in the corresponding spectra of **8** and **9**; see the results of the MM calculations below.



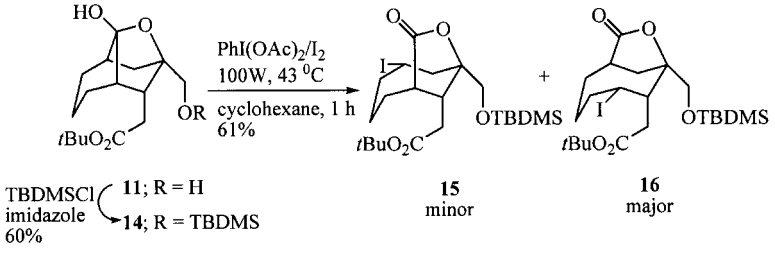
Scheme 2. Dihydroxylation of bicyclic ketones **2**–**5**.

Hemiacetals and hemiketals have been shown to undergo hypervalent-iodine-mediated photochemical alkoxy radical fragmentation (ARF) reactions in the presence of iodine. Pioneering work in this area was carried out by Suarez and co-workers.[11] Hence it was expected that the hemiketal **11** would be an ideal substrate to undergo the ARF reaction to provide a functionalized eight-membered ring. First, the primary hydroxy group of hemiketal **11** was protected as its TBDMS ether **14** by using TBDMSCl and imidazole (60%) following the standard procedure. Irradiation (100 W tungsten lamp, 43 °C) of the protected hemiketal **14** in the presence of $PhI(OAc)_2$ and I_2 for 1 h in cyclohexane under argon afforded the easily separable regioisomeric iodo lactones **15** and **16** in a ratio of 1:5, respectively, with an overall yield of 61% (Scheme 3).

The regio- and stereochemistry of lactones **15** and **16** were unambiguously established by analysis of their NMR spectra. The regiochemistry of the iodo substituents was clear from the multiplicity of the proton attached to the carbon bearing the iodine atom (H-3) (Figure 1). In lactone **15**, H-3 resonates at δ = 4.47 ppm as a dddd (J = 12.0, 11.0, 3.5, 2.0 Hz) indicating the presence of four neighbouring protons while in lactone **16**, H-3 resonates at δ = 4.87 ppm as a ddd (J = 9.5, 3.5, 1.0 Hz) as a result of its coupling with only three vicinal protons. The *cis* relationship between the iodine atom and the ester side-chain in lactone **15** was

Table 2. Dihydroxylation of bicyclic ketones **2**–**5**.

n	Ketone *endo* & *exo*	Diol	Hemiketal	Reaction time [h]	Isolated yield [%]	Ratio diol/hemiketal	Unreacted *exo* isomer [%]
1	**2**	**6**	**10**	12	55	0:100	14 (**2b**)
2	**3**	**7**	**11**	16	74	0:100	0 (**3b**)
3	**4**	**8**	**12**	16	51	100:0	28 (**4b**)
4	**5**	**9**	**13**	5	36	100:0	45 (**5b**)



Scheme 3. Stereoselective construction of eight-membered carbocyclic rings.

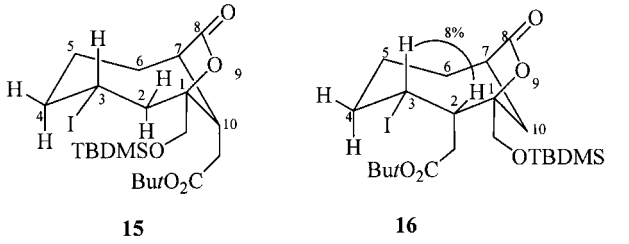
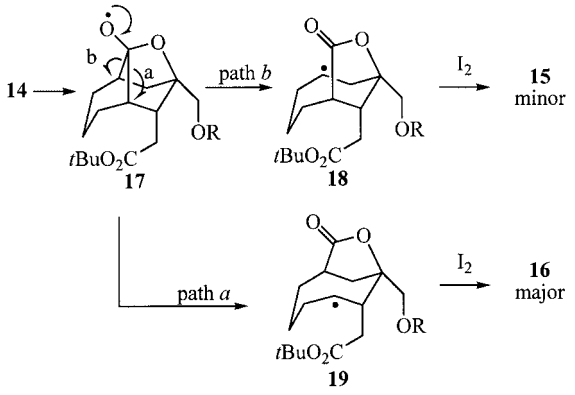


Figure 1. The regio- and stereochemistry of the iodo substituents of lactones **15** and **16**.

determined from the values of the coupling constants of H-3. The larger values of 12.0 and 11.0 Hz are in accordance with the expected diaxial couplings of H-3_{ax} with H-2_{ax} (δ = 2.37 ppm) and H-4_{ax}, respectively (Figure 1). The values of J = 3.5 and 2.0 Hz are consistent with the coupling of H-3_{ax} with H-2_{eq} and H-4_{eq}. In a similar way, the stereochemistry of iodine in lactone **16** was also determined from the values of the coupling constants of H-3. In addition, a NOE enhancement of 8% was observed between H-2 and H-3 in lactone **16,** which confirms the *cis* relationship between the iodine atom and the side-chains (Figure 1).

The ARF reaction of hemiketal **14** is believed to proceed via the initial formation of the alkoxy radical **17** followed by β-scission of the tricyclic ring, which can occur in two ways, to give carbon radicals **18** and **19**. Subsequent trapping by iodine afforded the regioisomeric iodo lactones **15** and **16** (Scheme 4). The preference for the cleavage step to take place by path *a* to form radical **19** rather than by step *b* to form **18** may be due to the noncovalent stabilization of the incipient radical by the neighboring carbonyl oxygen of the *tert*-butoxycarbonyl ester.

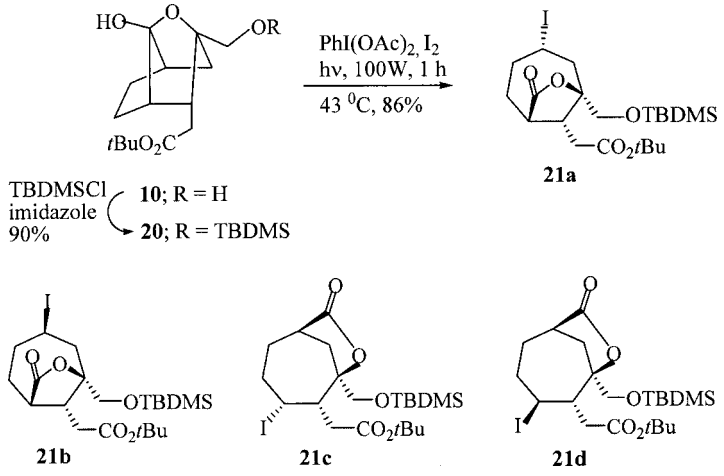


Scheme 4. Mechanism for the hypervalent-iodine-mediated ring-opening reaction of hemiketal **14**.

In a similar way, hemiketal **10**, obtained by dihydroxylation of bicyclic ketone **2a,** afforded seven-membered carbocyclic systems in good yield, but with low regio- and stereoselectivity. Protection of the primary hydroxy group of hemiketal **10** and subsequent ARF afforded highly functionalized cycloheptanes as a mixture of four isomers (**21a**, **21b**, **21c** and **21d** in a ratio of 1:2.5:4:7, respectively) in an overall yield of 86% (Scheme 5).

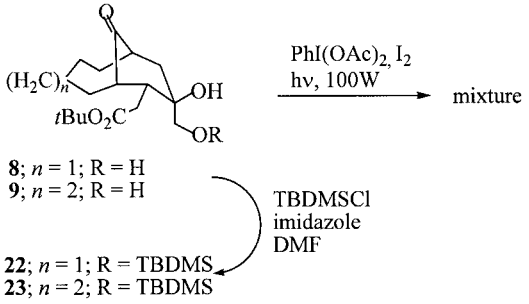
As described for **15** and **16**, the regiochemistry of these isomers (**21a–d)** was determined from the multiplicity pattern of the proton H-3 (geminal to I). In **21a**, H-3 resonates at δ = 4.32 ppm as a ddt while in **21b** it resonates at δ = 4.44 ppm as a dtd as a result of coupling with four vicinal protons. In **21c** and **21d**, H-3 has only three vicinal protons and hence appears as a ddd at δ = 4.67 and 4.64 ppm, respectively. The values of the coupling constants of H-3 are also consistent with the stereochemistry assigned to **21a–d**.

However, when the synthetic sequence was applied to the monoprotected keto diol **22**, which exists exclusively in the keto form, the expected nine-membered carbocyclic ring was not formed at all. Either the starting material was recovered or a complex mixture was obtained depending on the reaction conditions. This certainly indicates the necessity for a hemiketal functionality if the ARF reaction is to occur. Apparently, ketone–hemiketal equilibration is not favored in this system. In the absence of a hemiketal functionality, it is likely that the alkoxy radical initially formed from the alcohol, being unable to undergo the desired fragmentation, either remains inert or decomposes to give a complex mixture. The need for a hemiketal was further supported by



Scheme 5. Synthesis of seven-membered carbocyclic systems.

the failure of protected keto diol **23** to afford any of the expected ten-membered ring fragmentation products under identical reaction conditions (Scheme 6).



Scheme 6. Photochemical reaction of ketols **22** and **23**.

Conformational analysis provides some rationale for the ease of hemiketal formation or lack thereof in the keto alcohols **6**–**9**. First, an examination of the Dreiding models indicates that among the bicyclic ketones **2a**–**5a**, the bicyclo[3.3.1]nonanone **3a** is the least strained (two cyclohexanone chairs). After *exo* dihydroxylation of **3a**, the conformation of the six-membered ring containing the side-chain changes in order to prevent steric interactions of the CH_2OH group on the *endo* side. Hence, this cyclohexanone ring in **11** assumes a boat or semi-boat conformation, forcing the tertiary OH group into an axial position perfect for attack on the carbonyl group and formation of a hemiketal (see also Figure 2). A similar situation exists after *exo* dihydroxylation of **2a**. On the other hand, in the keto diol **8**, obtained by the dihydroxylation of **4a**, the six-membered ring is now so distorted (a skewed boat) that the tertiary OH group is too far from the carbonyl group to form a hemiketal, hence no ARF reaction is observed. The same also holds true for keto diol **9**.

These conclusions were supported by molecular mechanics (MM+) calculations.[12] The ease, as well as lack, of formation of hemiketals upon dihydroxylation of bicyclic ketones **2a**–**5a**, is clearly evident from the energy values obtained from the MM+ calculations (Table 3). Thus, the minimum energies of the keto diols **6a** and **7a** and their respective hemiketals **10** and **11** are nearly the same. In both of these cases (**6a** and **7a**), ARF cleavage was observed. By contrast, hemiketal **12** is much more strained than keto diol **8a** with the latter being more stable by 7 kcal mol^{-1}; the energy difference is even more pronounced in favor of keto diol **9a** (see Figure 2 and Table 3), which explains why neither **22** nor **23** underwent ARF cleavage. The results of the MM calculations also revealed that the distance between the bridgehead carbonyl carbon and the tertiary OH oxygen atom increases from **6a** to **9a** as follows: 3.81 Å for **6a**,

Table 3. MM+-calculated lowest energies of keto diols **6**–**9** and hemiketals **10**–**13**.

Diol	Energy [kcal mol^{-1}]	Hemiketal	Energy [kcal mol^{-1}]
6a	35.51	**10**	36.64
7a	37.47	**11**	37.55
8a	38.86	**12**	45.87
9a	39.03	**13**	47.53

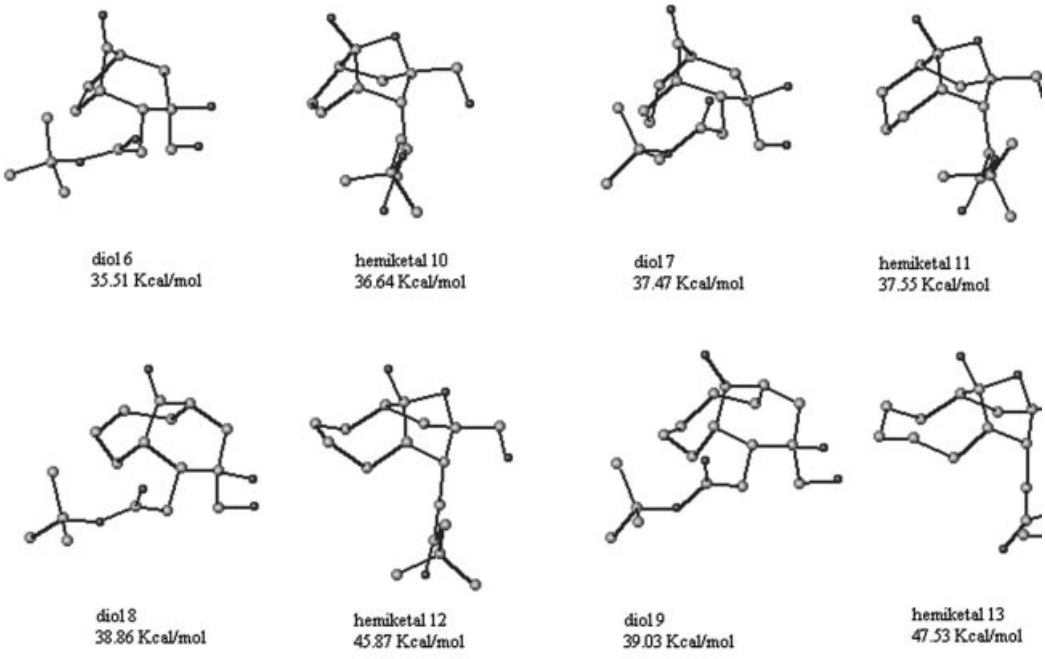


Figure 2. Low-energy conformations of keto diols and their hemiketals.

3.92 Å for **7a**, 4.03 Å for **8a** and 4.09 Å for **9a**, which is also in accord with the observed experimental results. However, the distance between the bridgehead carbonyl carbon and the primary hydroxy group (though too large for bonding) follows a reverse trend: 5.08 Å for **6a**, 4.97 Å for **7a**, 4.91 Å for **8a**, 4.86 Å for **9a**.

In the isomers in which the acetic ester side-chain is *exo*-oriented (**2b**, **4b** and **5b**), *exo* attack by OsO_4 is hindered, hence they remained intact upon attempted dihydroxylation. MM+ calculations also confirm this, as shown in Figure 3 by the minimum energy conformation of **2b**.

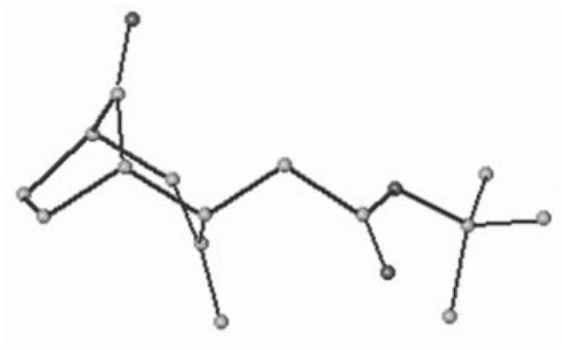
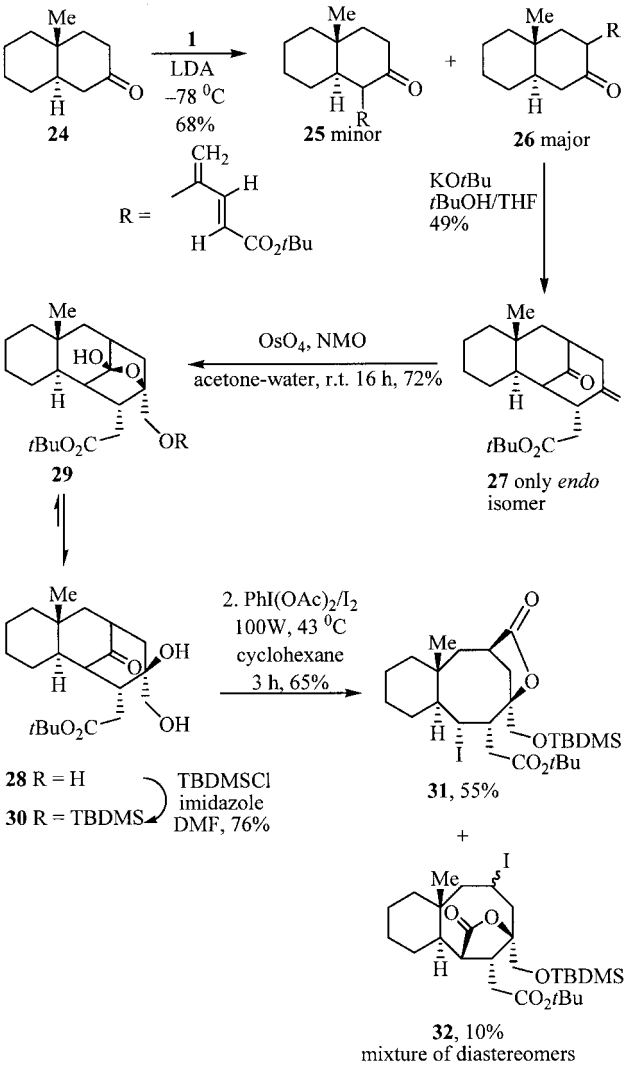


Figure 3. Low-energy conformation of *exo* compound **2b**.

Since the ring-opening reaction was only successful with hemiketals derived from cyclopentanone and cyclohexanone, we decided to focus our attention on other systems with a similar structural framework. We expected that application of our synthetic strategy to a tricyclic ketone such as **27** would lead to a functionalized bicyclo[6.4.0]dodecane framework. Interest in such systems have arisen owing to their presence in a variety of natural products, for example, taxol and variecolin.[1c] Initially, *trans*-methyldecalone **24** was chosen for the study since the *trans*-methyl ring junction is an integral part of these natural products.

The required tricyclic ketone **27** was synthesized from *trans*-methyldecalone **24** in two steps. Alkylation of **24** with lithium diisopropylamide and pentadienoic ester **1** afforded the easily separable regioisomeric decalones **25** and **26** in a ratio of 1:5.8, respectively, with an overall yield of 68%. The intramolecular Michael addition reaction of the major isomer **26** with KO*t*Bu yielded stereoselectively (only the *endo* isomer) the tricyclic ketone **27**. Dihydroxylation of the tricyclic ketone **27** proceeded smoothly to give the keto diol **28** in 72% yield, which was found to exist in equilibrium with its hemiketal form **29** (in a ratio of 86:14). Protection of the primary hydroxy group and subsequent ARF reaction afforded the bicyclo[6.4.0]decane system as a mixture of easily separable regioisomers **31** and **32** in a ratio of 5.5:1 with an overall yield of 65% (Scheme 7). Bicyclo[6.4.0]dodecane frameworks with a *trans*-methyl ring junction are prevalent in a number of natural products including taxol, and this method provides a convenient route to the construction of such ring systems with diverse functionality and scope for further elaboration.



Scheme 7. Construction of the *trans*-bicyclo[6.4.0]dodecane framework.

The regio- and stereochemistry of bicyclic lactone **31** were established from detailed ^{1}H NMR studies. In the ^{1}H NMR spectrum of **31**, H-2 appears as a dd (J = 3.5, 2.0 Hz) as a result of coupling with H-1 and H-2 (models indicate a dihedral angle of approx. 130°). Also, H-2 was found to have a NOE enhancement of 8.8% with H-3 and, more important, a 9% enhancement with the angular methyl group (Figure 4). The methyl group was found to have a NOE enhancement of 18% with H-2. These NOE studies confirm that the stereochemistry of iodine is *cis* with respect to the side-chains.

Having successfully synthesized the *trans*-fused bicyclo[6.4.0]dodecane framework, we next extended our methodology to the synthesis of *cis*-decalone **33**. Alkylation of *cis*-methyldecalone **33** with ester **1** in the presence of LDA provided the required substituted decalone as a mixture of two easily separable regioisomers **34** and **35** in a ratio of 1:4. The intramolecular Michael addition reaction of the major isomer **35** with potassium *tert*-butoxide proceeded stereoselectively to yield the tricyclic decalone **36** in 50%

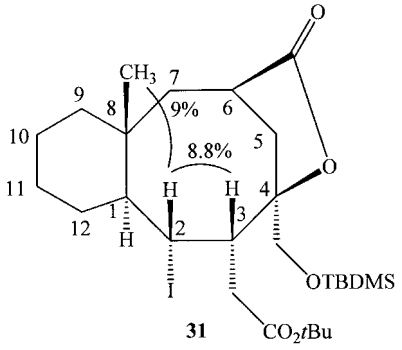
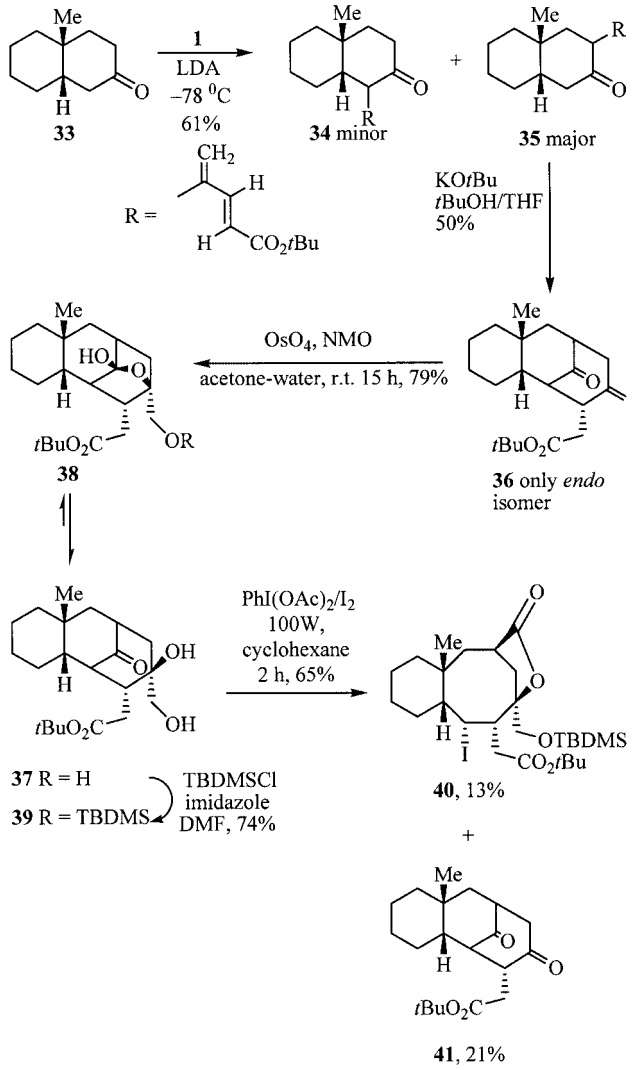


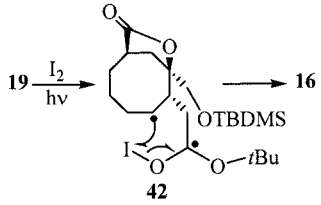
Figure 4. The regio- and stereochemistry of the iodo substituent of lactone **31**.

yield. Dihydroxylation of **36** afforded the diol **37**, which was in equilibrium with only a trace amount of its hemiketal **38**. Protection of the primary hydroxy group of **37** as its TBDMS ether **39** (74%) followed by the hypervalent-iodine-mediated ARF reaction afforded the *cis*-bicyclo[6.4.0]-dodecane **40** as a single stereo- and regioisomer, but in a low yield of 13%. Another product isolated in this reaction in 21% yield was identified as the dicarbonyl compound **41**, presumably formed by oxidative cleavage of the ketone **39** (Scheme 8). It is possible to envisage that cleavage of the alkoxy radical derived from **39** would provide ketone **41** and an ether-stabilized radical, which may further fragment to formaldehyde and the *tert*-butyldimethylsilyl radical trapped by iodine. The fact that the equilibrium in this system highly favors the diol **37** and not the hemiketal **38** probably results in the competing oxidative cleavage prevailing over the ARF reaction.



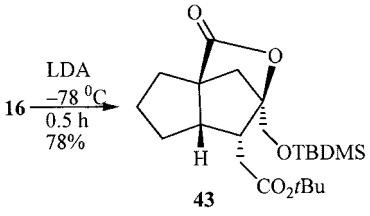
Scheme 8. Construction of the *cis*-bicyclo[6.4.0]dodecane framework.

Note that the introduction of the iodine atom into the major isomers **16**, **31** and **40** is likely to take place exclusively from the α side due to the presence of the vicinal *tert*-butoxycarbonyl group. A plausible explanation (though unprecedented) for this high stereoselectivity is that the iodine initially interacts with the *tert*-butoxycarbonyl group to form an iodoalkoxy radical such as **42**, and then the iodine atom is transferred to the ring from the α side (Scheme 9). However it is not clear yet why the preference for α-iodination does not hold for the seven-membered system **21**.



Scheme 9. Possible mechanism for the stereoselective introduction of an iodine atom into cyclooctanes.

Finally, we have also succeeded in synthesizing a diquinane from the cyclooctane **16**. Exposure of **16** to LDA at –78 °C afforded the diquinane **43** in 78% yield (Scheme 10).[10] The diquinane moiety with a carboxy group at the ring junction is prevalent in a number of natural products and the present route provides a convenient entry to such skeletons. However, a similar attempt with bicyclo[6.4.0]dodecane system **31** did not succeed probably due to ring strain in the resulting ring-fused *trans*-hydrindane.



Scheme 10. Synthesis of a diquinane.

Conclusions

In conclusion, we have successfully developed a strategy for the construction of polyfunctionalized eight-membered carbocyclic rings, including the bicyclo[6.4.0]dodecane

framework, by ARF reaction of hemiketals derived from cyclic ketones. High regio- and stereoselectivity was achieved in the synthesis of the cyclooctanes. Since the cyclooctane framework is prevalent in a number of biologically active natural products, these highly functionalized systems may provide an entry to such systems. As an illustration, the synthesis of a diquinane moiety was accomplished. The reaction was also successful for the synthesis of seven-membered carbocyclic systems, but with low regio- and stereoselectivity. Mild reaction conditions, moderate-to-high yields, high selectivity and functional-group tolerance make this route attractive for the construction of medium-sized carbocycles. MM+ calculations are consistent with successful ARF cleavage in the formation of seven- and eight-membered rings and the lack of such cleavage in the formation of nine- and ten-membered rings of these bicyclic systems. This behavior has been correlated with the presence or absence of the hemiketal function.

Experimental Section

General: All solvents were dried according to standard procedures. All fine chemicals were purchased from Sigma, Aldrich or Fluka and were used as such without further purification. NMR spectra were recorded with a Bruker 300 MHz instrument in $CDCl_3$ (unless otherwise stated) and chemical shifts are reported relative to TMS. Mass spectra were recorded on a Finnigan MAT 4510 mass spectrometer. All new compounds, except those for which melting points are given, were isolated as oils.

General Procedure for the Dihydroxylation of 2–5:[10] *N*-Methylmorpholine *N*-oxide (NMO) monohydrate (0.5 mmol) was added to a solution of bicyclic ketone **2**–**5** (mixture of *endo* and *exo* isomers) (0.4 mmol) in acetone (0.5 mL) and water (0.5 mL). A 3% solution (0.1 mL) of OsO_4 (3 mg, 0.011 mmol) in water was then added and the reaction mixture was vigorously stirred at room temperature for the specified time (Table 1). A 1:1 mixture of sodium dithionate and florisil in water (1 mL) was added to the reaction mixture and stirred for 15 min. The reaction mixture was then passed through a small column of Celite and washed several times with acetone. Acetone was evaporated under vacuum and the residue was extracted with CH_2Cl_2 (4 × 10 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated. Column chromatography (hexane/ethyl acetate, 1:1) afforded the diols **6**–**9**/ hemiketals **10**–**13**.

Hemiketal 10: Hemiketal **10** was obtained from bicyclic ketone **2** (**2a** + **2b**) in 55% yield following the general procedure, along with 14% of unreacted *exo* isomer **2b**. ^{1}H NMR: δ = 3.74 (d, ^1J = 13 Hz, 1 H, CH_2OH), 3.63 (d, ^1J = 13 Hz, 1 H, CH_2OH), 2.89–2.77 (m, 1 H), 2.32–2.26 (m, 1 H), 2.23 (dd, ^1J = 7.5, 5.0 Hz, 1 H), 2.20–1.88 (m, 4 H), 1.74–1.43 (m, 13 H with *tert*-butyl signals superimposed on it), 1.30 ppm (dd, ^1J = 13.0, 2.5 Hz, 1 H). ^{13}C NMR: δ = 172.0 (s), 118.2 (s), 82.8 (s), 81.0 (s), 62.4 (t), 45.4 (d), 43.2 (d), 41.2 (d), 37.9 (t), 33.0 (t), 28.1 (t), 27.9 (q), 21.9 ppm (t). MS (CI): *m*/*z* (%) = 285 [MH]$^+$, 229, 193. HRMS: found [MH]$^+$ 285.165780; $C_{15}H_{25}O_5$ requires 285.170199. The absence of the ketone carbonyl signal in the ^{13}C NMR spectrum clearly suggests that the diol exists in the hemiketal form **10**.

Hemiketal 11: Hemiketal **11** was obtained from bicyclic ketone **3a** in 74% yield following the general procedure. ^{1}H NMR: δ = 3.70 (d, ^1J = 13 Hz, 1 H, CH_2OH), 3.54 (d, ^1J = 13 Hz, 1 H, CH_2OH), 2.86 (dddd, ^1J = 12.0, 8.5, 6.0, 2.5 Hz, 1 H), 2.47 (dd, ^1J = 17.0, 6.0 Hz, 1 H, CH_2CO$_2t$Bu), 2.30 (dd, ^1J = 17.0, 8.5 Hz, 1 H, CH_2CO$_2t$Bu), 2.28–2.12 (m, 2 H), 1.76 (ddd, ^1J = 13.0, 12.0, 2.5 Hz, 1 H), 1.70–1.58 (m, 4 H), 1.45 (dd, ^1J = 13.0, 5.0 Hz, 1 H), 1.45 (m, 10 H with the *tert*-butyl signals superimposed on it), 1.32–1.19 ppm (m, 1 H). ^{13}C NMR: δ = 173.1 (s), 106.3 (s), 83.6 (s), 81.4 (s), 63.0 (t), 41.3 (d), 40.6 (d), 40.0 (d), 31.9 (t), 29.9 (t), 28.0 (q), 24.1 (t), 22.4 (t), 17.6 ppm (t). MS (DCI): *m*/*z* (%) = 299 [MH]$^+$, 243, 207. HRMS: found [MH]$^+$ 299.180474; $C_{16}H_{27}O_5$ requires 299.185849. The absence of ketone carbonyl signal in the ^{13}C NMR spectrum clearly suggests that the diol exists in the hemiketal form **11**.

Keto Diol 8: Keto diol **8** was obtained from bicyclic ketone **4** (**4a** + **4b**) in 51% yield following the general procedure, along with 28% of unreacted *exo* isomer **4b**. ^{1}H NMR: δ = 3.56 (d, ^1J = 11 Hz, 1 H, CH_2OH), 3.42 (d, ^1J = 11 Hz, 1 H, CH_2OH), 3.27 (br. s, 1 H, OH), 2.84–2.59 (m, 4 H), 2.46–2.32 (m, 2 H), 2.09 (dd, ^1J = 14.5, 11.5 Hz, 1 H), 1.88–1.65 (m, 5 H), 1.57–1.30 (m, 12 H with the *tert*-butyl signals superimposed), 1.29–1.02 ppm (m, 1 H). ^{13}C NMR: δ = 217.6 (s), 171.8 (s), 81.0 (s), 73.7 (s), 67.7 (t), 48.2 (d), 44.8 (d), 44.7 (d), 33.6 (t), 30.9 (t), 29.1 (t), 28.0 (q), 26.6 (t), 25.4 (t), 24.2 ppm (t). MS (DCI): *m*/*z* (%) = 313 [MH]$^+$, 257, 239, 221, 203. HRMS: found [MH]$^+$ 313.198368; $C_{17}H_{29}O_5$ requires 313.201499. The presence of a signal at δ = 217.63 ppm in the ^{13}C NMR clearly shows that the molecule is present in the keto diol form.

Keto Diol 9: Keto diol **9** was obtained from bicyclic ketone **5** (**5a** + **5b**) in 36% yield following the general procedure, along with 45% of unreacted *exo* isomer **5b**. ^{1}H NMR: δ = 3.66 (d, ^1J = 11.5 Hz, 1 H, CH_2OH), 3.58 (d, ^1J = 11 Hz, 1 H, CH_2OH), 3.49 (br. s, OH), 2.75 (dd, ^1J = 16.5, 9.0 Hz, 1 H), 2.65–2.55 (m, 1 H), 2.45–2.36 (m, 1 H), 2.35–2.24 (m, 2 H), 2.10–1.94 (m, 1 H), 1.93–1.30 ppm (m, 21 H with the *tert*-butyl signals superimposed). ^{13}C NMR: δ = 219.6 (s), 173.2 (s), 81.5 (s), 73.1 (s), 68.5 (t), 52.5 (d), 45.6 (d), 44.2 (d), 36.6 (t), 34.8 (t), 32.8 (t), 28.0 (q), 27.1 (t), 24.5 (t), 24.4 (t), 21.7 ppm (t). MS (DCI): *m*/*z* (%) = 327 [MH]$^+$, 299, 271, 253, 235, 217. HRMS: found [MH]$^+$ 327.212722; $C_{18}H_{31}O_5$ requires 327.217149. The presence of a signal at δ = 219.69 ppm in the ^{13}C NMR spectrum clearly shows that the molecule is present in the keto diol form.

General Procedure for the Selective Protection of the Primary Hydroxy Group of Hemiketals 10 and 11 and Diols 8 and 9: Imidazole (0.37 mmol) and TBDMSCl (0.255 mmol) were added to a solution of the hemiketal (**10**, **11**) or the diol (**8**, **9**) (0.17 mmol) in dry DMF (1 mL) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water, dried with anhydrous $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane/ethyl acetate, 9:1) afforded the monosilyl ether.

Compound 20: Compound **20** was obtained from the hemiketal **10** in 90% yield. ^{1}H NMR: δ = 4.48 (br. s, 1 H, OH), 3.74 (d, ^1J = 12 Hz, 1 H, CH_2OH), 3.68 (d, ^1J = 12 Hz, 1 H, CH_2OH), 2.69 (dddd, ^1J = 13.0, 12.0, 4.0, 2.5 Hz, 1 H), 2.35 (dd, ^1J = 12.5, 2.5 Hz, 1 H, CH_2CO$_2t$Bu), 2.30–2.23 (m, 1 H), 2.11 (dd, ^1J = 12.5, 9.0 Hz, 1 H, CH_2CO$_2t$Bu), 2.08–1.82 (m, 4 H), 1.69–1.35 (m, 11 H with the *tert*-butyl signals superimposed), 1.29–1.21 (m, 1 H), 0.90 (s, 9 H, *t*Bu), 0.07–0.05 ppm (2s, 6 H, 2CH_3). ^{13}C NMR: δ = 171.4 (s), 118.3 (s), 82.2 (s), 80.4 (s), 63.8 (t), 45.6 (d), 43.2 (d), 42.8 (d), 38.6 (t), 33.3 (t), 28.3 (t), 28.0 (q), 25.8 (q), 21.9 (t), 18.3 (s), –5.4 (q), –5.5 ppm (q). MS (CI): *m*/*z* (%) = 399 [MH]$^+$, 343, 325, 267, 193. HRMS: found [MH]$^+$ 399.255905; $C_{21}H_{39}O_5Si$ requires 399.256678.

Compound 14: Compound **14** was obtained from the hemiketal **11** in 60% yield. M.p. 112 °C. ^{1}H NMR: δ = 4.61 (br. s, 1 H, OH), 3.69 (s, 2 H), 2.81–2.69 (m, 1 H), 2.50–2.07 (m, 4 H), 1.90–1.77 (m, 1 H), 1.50–1.30 (m, 16 H), 0.90 (s, 9 H), 0.05 ppm (s, 6 H). ^{13}C NMR: δ = 172.0 (s), 106.5 (s), 82.7 (s), 80.4 (s), 64.4 (t), 42.4 (d), 41.0 (d), 40.8 (d), 32.3 (t), 29.9 (t), 28.0 (q), 25.9 (q), 24.13 (t), 22.1 (t), 18.1 (s), 17.9 (t), –5.41 (q), –5.46 ppm (q). MS (CI): *m*/*z* (%) = 413 $[MH]^+$, 357, 339, 299, 280, 207. HRMS: found $[MH]^+$ 413.268093; $C_{22}H_{41}O_5Si$ requires 413.272328.

Compound 22: Compound **22** was obtained from the diol **8** in 77% yield following the general procedure. ^{1}H NMR: δ = 3.51 (d, ^1J = 10 Hz, 1 H, C*H*$_2$OTBDMS), 3.39 (d, ^1J = 10 Hz, 1 H, C*H*$_2$OTBDMS), 2.72–2.51 (m, 4 H), 2.40–2.25 (m, 1 H), 2.18 (dd, ^1J = 14.0, 10.5 Hz, 1 H), 1.90–1.38 (m, 19 H with the *tert*-butyl signals superimposed), 0.9 (s, 9 H, *t*Bu), 0. 1 ppm (s, 6 H, 2C*H*$_3$). ^{13}C NMR: δ = 216.8 (s), 171.6 (s), 80.7 (s), 73.2 (s), 68.1 (t), 48.5 (d), 45.6 (d), 44.6 (d), 33.8 (t), 31.0 (t), 29.3 (t), 28.0 (q), 26.6 (t), 25.7 (q), 25.4 (t), 23.9 (t), 18.1 (s), –5.54 ppm (2q superimposed). MS (DCI): *m*/*z* (%) = 427 $[MH]^+$, 353, 294, 221. HRMS: found $[MH]^+$ 427.277603; $C_{23}H_{43}O_5Si$ requires 427.287978.

Compound 23: Compound **23** was obtained from the diol **9** in 76% yield following the general procedure. ^{1}H NMR: δ = 3.53 (d, ^1J = 10 Hz, 1 H, C*H*$_2$OTBDMS), 3.47 (d, ^1J = 10 Hz, 1 H, C*H*$_2$OTBDMS), 3.13 (br. s, 1 H), 2.87 (dd, ^1J = 16.5, 8.5 Hz, 1 H, C*H*$_2$CO$_2$*t*Bu), 2.81–2.70 (m, 1 H), 2.67–2.47 (m, 2 H), 2.41–2.32 (m, 1 H), 2.25 (dd, ^1J = 16.5, 7.0 Hz, 1 H, C*H*$_2$CO$_2$*t*Bu), 2.12–1.93 (m, 2 H), 1.83–1.30 (m, 18 H with the *tert*-butyl signals superimposed), 0.93 (s, 9 H, *t*Bu), 0.104 ppm (s, 6 H, 2C*H*$_3$). ^{13}C NMR: δ = 220.2 (s), 172.9 (s), 81.0 (s), 73.0 (s), 68.2 (t), 52.4 (d), 46.1 (d), 43.8 (d), 35.9 (t), 34.4 (t), 33.1 (t), 28.0 (q), 26.7 (t), 25.8 (q), 24.4 (t), 24.2 (t), 21.3 (t), 18.1 (s), –5.53 (q), –5.57 ppm (q). MS (DCI): *m*/*z* (%) = 441 $[MH]^+$, 413, 367, 235. HRMS: found $[MH]^+$ 441.302362; $C_{24}H_{45}O_5Si$ requires 441.303628.

General Procedure for Suarez's ARF Reaction: PhI(OAc)$_2$ (1.29 mmol) and I$_2$ (1.29 mmol) were added at once to a solution of protected hemiketal (0.72 mmol) in dry cyclohexane (85 mL) under argon. The resulting reaction mixture was irradiated with a 100-W tungsten filament lamp (internal temperature, 43 °C) for a specified time, after which the reaction mixture was poured into a 1:1 mixture of ether and aqueous $NaHSO_3$ solution. The organic layer was separated, washed with $NaHSO_3$ solution, dried with anhydrous $MgSO_4$, filtered and concentrated. Column chromatography over silica gel using petroleum ether and ethyl acetate (9:1) afforded the products.

Synthesis of Functionalized Cyclooctanes 15 and 16: After irradiation for 1 h, monosilyl ether **14** (295 mg, 0.72 mmol) afforded a mixture of regioisomers **15** and **16** in a ratio of 1:5 in an overall yield of 61% (235 mg).

Compound 15: ^{1}H NMR: δ = 4.47 (dddd, ^1J = 12.0, 11.0, 3.5, 2.0 Hz, 1 H, H-3), 3.52 (d, ^1J = 10.5 Hz, 1 H, C*H*$_2$OTBDMS), 3.43 (d, ^1J = 10.5 Hz, 1 H, C*H*$_2$OTBDMS), 3.18 (td, ^1J = 10.5, 5.0 Hz, 1 H), 3.08 (ddd, ^1J = 10.5, 7.5, 1.5 Hz, 1 H), 2.83 (ddd, ^1J = 15.0, 10.0, 2.0 Hz, 1 H, C*H*$_2$CO$_2$*t*Bu), 2.72–2.46 (m, 2 H), 2.37 (dd, ^1J = 15.0, 12.0 Hz, 1 H, C*H*$_2$CO$_2$*t*Bu), 2.20–1.99 (m, 2 H), 1.79–1.58 (m, 3 H), 1.57–1.37 (m, 10 H with the *tert*-butyl signals superimposed), 0.89 (s, 9 H, *t*Bu), 0.082 (s, 3 H, CH$_3$), 0.068 ppm (s, 3 H, CH$_3$). ^{13}C NMR: δ = 177.0 (s), 170.1 (s), 88.2 (s), 81.4 (s), 69.3 (t), 45.3 (t), 42.2 (d), 41.3 (t), 36.6 (d), 34.1 (t), 29.3 (d), 28.0 (q), 27.0 (t), 25.7 (q), 24.9 (t), 18.1 (s), –5.2 ppm (2q superimposed). MS (DCI): *m*/*z* (%) = 539 $[MH]^+$, 483, 465, 425, 355. HRMS: found $[MH]^+$ 539.167411; $C_{22}H_{40}O_5SiI$ requires 539.168980.

Compound 16: M.p. 142–143 °C. ^{1}H NMR: δ = 4.87 (ddd, ^1J = 9.5, 3.5, 1.0 Hz, 1 H, H-3), 3.61 (d, ^1J = 11.0 Hz, 1 H, C*H*$_2$OTBDMS), 3.38 (d, ^1J = 11.0 Hz, 1 H, C*H*$_2$OTBDMS), 3.05 (dt, ^1J = 5.0, 3.5 Hz, 1 H), 2.91 (ddt, ^1J = 11.5, 5.5, 2.5 Hz, 1 H), 2.83 (dd, ^1J = 17.5, 3.5 Hz, 1 H, C*H*$_2$CO$_2$*t*Bu), 2.73–2.58 (m, 2 H), 2.25 (dd, ^1J = 17.5, 5.0 Hz, 1 H, C*H*$_2$CO$_2$*t*Bu), 2.23–2.13 (m, 2 H), 1.89–1.77 (m, 2 H), 1.62–1.40 (m, 11 H with the *tert*-butyl signals superimposed), 0.86 (s, 9 H, *t*Bu), 0.048 (s, 3 H, CH$_3$), 0.044 ppm (s, 3 H, CH$_3$). ^{13}C NMR (75 MHz): δ = 178.0 (s), 170.8 (s), 88.6 (s), 81.2 (s), 67.1 (t), 47.4 (d), 39.3 (d), 36.1 (d), 36.1 (t), 35.7 (t), 32.4 (t), 28.0 (q), 28.0 (t), 27.8 (t), 25.7 (q), 18.1 (s), –5.3 (q), –5.5 ppm (q). HRMS: found $[MH]^+$ 539.168978; $C_{22}H_{40}O_5SiI$ requires 539.168980.

Synthesis of Functionalized Cycloheptanes 21a–d: Monosilyl ether **20** (240 mg), upon ARF reaction for 1 h, produced **21a–d** in a ratio of 1:2.5:4:7, respectively, in an overall yield of 86%. All the isomers were separated by column chromatography and their stereo- and regiochemistry were unambiguously assigned by detailed NMR studies.

Compound 21a: ^{1}H NMR: δ = 4.32 (ddt, ^1J = 13.0, 12.0, 3.0 Hz, 1 H, H-3), 3.71 (d, ^1J = 11.0 Hz, 1 H, C*H*$_2$OTBDMS), 3.59 (d, ^1J = 11.0 Hz, 1 H, C*H*$_2$OTBDMS), 3.08 (dd, ^1J = 15.0, 8.0 Hz, 1 H), 2.83 (td, ^1J = 8.0, 1.5 Hz, 1 H), 2.74–2.61 (m, 2 H), 2.60–2.50 (m, 2 H), 2.42–2.22 (m, 2 H), 2.14 (dddd, ^1J = 15.0, 11.0, 8.5, 2.0 Hz, 1 H), 1.86 (dt, ^1J = 15.0, 7.5 Hz, 1 H), 1.45 (s, 9 H, *t*Bu), 0.89 (s, 9 H, *t*Bu), 0.05 ppm (2 s, 6 H, CH$_3$). ^{13}C NMR: δ = 179.4 (s), 170.1 (s), 89.7 (s), 81.4 (s), 66.5 (t), 47.5 (t), 41.3 (d), 40.3 (d), 40.2 (t), 32.5 (t), 28.0 (q), 27.0 (t), 25.8 (q), 20.5 (d), 18.1 (s), –5.3 (q), –5.4 ppm (q). MS (CI): *m*/*z* (%) = 525 $[MH]^+$, 469, 411, 341. HRMS: found $[MH]^+$ 525.146442; $C_{21}H_{38}O_5SiI$ requires 525.153330.

Compound 21b: ^{1}H NMR: δ = 4.44 (dtd, ^1J = 13.0, 9.0, 2.5 Hz, 1 H, H-3), 3.58 (s, 2 H), 3.05 (ddd, ^1J = 11.0, 7.0, 4.0 Hz, 1 H), 2.90 (dt, ^1J = 7.0, 4.0 Hz, 1 H), 2.68–2.50 (m, 5 H), 2.37–2.21 (m, 1 H), 1.89–1.82 (m, 2 H), 1.45 (s, 9 H, *t*Bu), 0.89 (s, 9 H, *t*Bu), 0.08 (s, 3 H, CH$_3$), 0.073 ppm (s, 3 H, CH$_3$). ^{13}C NMR: δ = 176.3 (s), 170.0 (s), 90.0 (s), 81.5 (s), 67.9 (t), 46.8 (t), 43.5 (d), 41.1 (d), 37.8 (t), 31.5 (t), 28.0 (q), 27.3 (t), 25.8 (q), 23.2 (d), 18.2 (s), –5.1 ppm (2q superimposed). MS (CI): *m*/*z* (%) = 525 $[MH]^+$, 469, 341, 218. HRMS: found $[MH]^+$ 525.127240; $C_{21}H_{38}O_5SiI$ requires 525.153330.

Compound 21c: ^{1}H NMR: δ = 4.67 (ddd, ^1J = 11.5, 4.0, 1.5 Hz, 1 H, H-3), 3.74 (d, ^1J = 11.5 Hz, 1 H, C*H*$_2$OTBDMS), 3.56 (d, ^1J = 11.5 Hz, 1 H, C*H*$_2$OTBDMS), 2.94–2.87 (m, 1 H), 2.75 (dd, ^1J = 17.5, 3.5 Hz, 1 H, C*H*$_2$CO$_2$*t*Bu), 2.74 (td, ^1J = 8.5, 1.0 Hz, 1 H), 2.40 (dd, ^1J = 17.5, 5.5 Hz, 1 H, C*H*$_2$CO$_2$*t*Bu), 2.40–2.30 (m, 2 H), 2.19 (dtd, ^1J = 15.0, 11.5, 5.5 Hz, 1 H), 2.05 (ddd, ^1J = 14.0, 11.0, 6.0 Hz, 1 H), 1.95–1.75 (m, 2 H), 1.50 (s, 9 H, *t*Bu), 0.9 (s, 9 H, *t*Bu), 0.05 ppm (s, 6 H, 2CH$_3$). ^{13}C NMR: δ = 180.0 (s), 170.6 (s), 89.9 (s), 81.1 (s), 66.0 (t), 47.7 (d), 41.2 (d), 38.7 (t), 36.3 (t), 33.8 (t), 29.4 (t), 27.8 (q), 26.4 (d), 25.8 (q), 18.2 (s), –5.3 (q), –5.4 ppm (q). MS (CI): *m*/*z* (%) = 525 $[MH]^+$, 469, 411, 341, 165. HRMS: found $[MH]^+$ 525.132565; $C_{21}H_{38}O_5SiI$ requires 525.153330.

Compound 21d: ^{1}H NMR: δ = 4.64 (ddd, ^1J = 12.0, 9.0, 2.0 Hz, 1 H, H-3), 3.80 (d, ^1J = 11.5 Hz, 1 H, C*H*$_2$OTBDMS), 3.57 (d, ^1J = 11.5 Hz, 1 H, C*H*$_2$OTBDMS), 2.86–2.65 (m, 5 H), 2.38 (dtd, ^1J = 15.0, 12.0, 3.5 Hz, 1 H), 2.20–2.11 (m, 1 H), 1.97 (d, ^1J = 13.0 Hz, 1 H), 1.92 (dq, ^1J = 14.0, 4.5 Hz, 1 H), 1.69 (ddt, ^1J = 14.0, 12.0, 3.5 Hz, 1 H), 1.50 (s, 9 H, *t*Bu), 0.90 (s, 9 H, *t*Bu), 0.1 ppm (2 s, 6 H, 2CH$_3$). ^{13}C NMR: δ = 177.1 (s), 170.8 (s), 89.5 (s), 81.3 (s), 68.0 (t), 51.1 (d), 40.7 (d), 38.2 (t), 37.8 (t), 35.11 (d), 33.5 (t), 30.4 (t), 28.1 (q), 25.8 (q), 18.2 (s), –5.3 (q), –5.4 ppm (q). MS (CI): *m*/*z* (%)

= 525 $[MH]^+$, 469, 451, 411, 341. HRMS: found $[MH]^+$ 525.135898; $C_{21}H_{38}O_5SiI$ requires 525.153330.

Synthesis of the *trans*-Bicyclo[6.4.0]dodecane System 31

Alkylation of *trans*-Methyldecalone 24 with Pentadienoic Ester 1: LDA (2.77 mmol) was formed at 0 °C by addition of BuLi (2.77 mmol, 1.85 mL of a 1.5 M solution) to diisopropylamine (2.77 mmol, 279 mg, 0.39 mL) in THF (2 mL). The LDA solution was then cooled to –78 °C and decalone **24** (355 mg, 2.13 mmol) in THF (1.5 mL) was injected into it. The reaction mixture was stirred at –78 °C for 0.5 h and then warmed to –20 °C. After another 0.5 h, it was again cooled to –78 °C and mesylate **1** (2.35 mmol, 615 mg) in dry THF (1.5 mL) was injected into it. The reaction mixture was then stirred at –78 °C for 0.5 h, warmed to –30 °C and stirred for 2 h, after which it was quenched with aq. NH_4Cl and extracted with CH_2Cl_2, dried with anhydrous $MgSO_4$, filtered and concentrated. Column chromatography (hexane/ethyl acetate, 9:1) afforded two regioisomers **25** and **26** in a ratio of 1:5.8 in an overall yield of 68% and their regiochemistry confirmed by spectroscopic data.

Compound 25: ^{1}H NMR: δ = 7.17 (d, ^1J = 16.0 Hz, 1 H, C*H*=CH–CO_2tBu), 5.82 (d, ^1J = 16.0 Hz, 1 H, CH=C*H*–CO_2tBu), 5.34 (s, 1 H, =CH_2), 5.22 (s, 1 H, =CH_2), 2.72 (dd, ^1J = 15.5, 7.5 Hz, 1 H, CH_2CO_2tBu), 2.60–2.40 (m, 2 H), 2.32 (ddd, ^1J = 14.0, 5.0, 2.5 Hz, 1 H), 2.14 (dd, ^1J = 15.5, 3.5 Hz, 1 H, CH_2CO_2tBu), 1.83–1.60 (m, 4 H), 1.61–1.40 (m, 11 H with the *tert*-butyl signals superimposed), 1.40–0.80 ppm (m, 8 H with the methyl signals superimposed). ^{13}C NMR: δ = 211.4 (s), 166.4 (s), 146.0 (d), 143.5 (s), 122.8 (t), 119.6 (d), 80.2 (s), 51.0 (d), 49.5 (d), 42.7 (t), 41.0 (t), 39.6 (t), 34.3 (s), 31.8 (t), 28.1 (q), 27.0 (t), 26.2 (t), 21.2 (t), 16.5 ppm (q). MS (CI): *m*/*z* (%) = 333 $[MH]^+$, 317, 306, 277, 259. HRMS: found $[MH]^+$ 333.233208; $C_{21}H_{33}O_3$ requires 333.242970.

Compound 26: ^{1}H NMR: δ = 7.18 (d, ^1J = 16.0 Hz, 1 H, C*H*=CH–CO_2tBu), 5.78 (d, ^1J = 16.0 Hz, 1 H, CH=C*H*–CO_2tBu), 5.39 (s, 1 H, = CH_2), 5.25 (s, 1 H, =CH_2), 2.99 (ddd, ^1J = 14.5, 4.5, 1.5 Hz, 1 H), 2.58 (dddd, ^1J = 13.5, 8.0, 5.5, 4.5 Hz, 1 H), 2.26 (ddd, ^1J = 14.0, 13.5, 1.0 Hz, 1 H), 2.14 (dd, ^1J = 14.0, 4.0 Hz, 1 H, CH_2CO_2tBu), 1.93 (dd, ^1J = 14.0, 9.0 Hz, 1 H, CH_2CO_2tBu), 1.75 (dd, ^1J = 13.0, 5.5 Hz, 1 H), 1.74–1.69 (m, 1 H), 1.60–1.41 (m, 14 H with the *tert*-butyl signals superimposed), 1.40–1.20 (m, 3 H), 1.19–1.02 ppm (m, 4 H with the methyl signals superimposed). ^{13}C NMR: δ = 210.89 (s), 166.3 (s), 145.2 (d), 142.7 (s), 123.7 (t), 120.3 (d), 80.4 (s), 48.6 (t), 46.1 (d), 45.3 (d), 44.7 (t), 40.2 (t), 33.9 (s), 31.3 (t), 28.8 (t), 28.2 (q), 26.0 (t), 21.4 (t), 15.7 ppm (q). MS (CI): *m*/*z* (%) = 333 $[MH]^+$, 317, 304, 277, 259. HRMS: found $[MH]^+$ 333.230398; $C_{21}H_{33}O_3$ requires 333.242970.

Intramolecular Michael Addition Reaction of Compound 26: Potassium *tert*-butoxide was freshly prepared by the addition of potassium metal (1.17 mmol, 46 mg) to dry *tert*-butyl alcohol (1.5 mL) under argon. Compound **26** (0.9 mmol, 290 mg) was dissolved in dry THF (1.5 mL) and cooled to 0 °C. Potassium *tert*-butoxide in *tert*-butyl alcohol was injected dropwise into this solution. After 15 min at 0 °C, the reaction mixture was warmed to room temperature and stirred for 1 h. It was then quenched with aq. NH_4Cl and extracted with CH_2Cl_2, dried with anhydrous $MgSO_4$, filtered and concentrated. Column chromatography (hexane/ethyl acetate, 9:1) afforded only the *endo* isomer **27** in 49% yield (142 mg). ^{1}H NMR: δ = 5.06 (s, 1 H, =CH_2), 4.92 (s, 1 H, =CH_2), 2.93–2.84 (m, 1 H), 2.63–2.47 (m, 3 H), 2.36 (dd, ^1J = 13.5, 3.0 Hz, 1 H), 2.24 (dd, ^1J = 15.5, 7.5 Hz, 1 H), 2.03–1.98 (m, 1 H), 1.86 (dd, ^1J = 13.5, 10.0 Hz, 1 H), 1.73–1.62 (m, 1 H), 1.58–1.10 (m, 17 H with the *tert*-butyl signals superimposed), 1.09–0.96 (m, 1 H), 0.79 ppm (s, 3 H, CH_3). ^{13}C NMR: δ = 220.4 (s), 170.7 (s), 143.0 (s), 113.8 (t), 80.8 (s), 54.6 (d), 47.3 (d), 45.5 (t), 45.2 (t), 44.9 (d), 44.6 (d), 40.8 (t), 36.5 (t), 31.9 (s), 30.2 (t), 28.0 (q), 26.0 (t), 21.3 (t), 18.8 ppm (q). MS (EI): *m*/*z* (%) = 332 $[M]^+$, 276, 201, 166. HRMS: found $[M]^+$ 332.236628; $C_{21}H_{32}O_3$ requires 332.235145.

Dihydroxylation of Compound 27: Following the general procedure, compound **27** (126 mg, 0.38 mmol) was dihydroxylated to yield an inseparable equilibrium mixture of diol **28** and hemiketal **29** in 72% yield (100 mg). From the ^{1}H NMR spectrum the ratio of diol and hemiketal was calculated to be 86:14. ^{1}H NMR (signals of only the diol **28** are given as the NMR spectrum is complicated owing to the mixture of diol **28** and hemiketal **29**): δ = 3.95 (m, 2 H), 3.80 (br. s, 1 H, OH), 2.80 (br. s, 1 H, OH), 2.80–2.55 (m, 4 H), 2.30 (dd, ^1J = 16.0, 8.0 Hz, 1 H), 2.00–1.65 (m, 6 H), 1.52–1.08 (m, 16 H with the *tert*-butyl signals superimposed), 0.81 ppm (s, 3 H, CH_3). ^{13}C NMR: δ = 221.3 (s), 172.3 (s), 81.5 (s), 73.0 (s), 67.3 (t), 52.7 (d), 51.9 (d), 45.3 (d), 44.6 (t), 43.9 (t), 42.7 (d), 41.4 (t), 34.8 (t), 32.9 (s), 30.7 (t), 28.0 (q), 26.0 (t), 21.2 (t), 18.9 ppm (q). MS (CI): *m*/*z* (%) = 367 $[MH]^+$, 311, 293, 261, 236, 164. HRMS: found $[MH]^+$ 367.267410; $C_{21}H_{35}O_5$ requires 367.268450.

***tert*-Butyldimethylsilylation of a Mixture of Diol 28 and Hemiketal 29:** The inseparable mixture of the diol **28** and hemiketal **29** (0.21 mmol, 77 mg) on reaction with imidazole (0.46 mmol, 32 mg) and TBDMSCl (0.32 mmol, 48 mg) in dry DMF (1 mL) yielded the monosilyl ether **30** (as a mixture of keto diol and hemiketal) in 76% yield (77 mg). ^{1}H NMR (signals of the protected diol **30** only are given): δ = 4.09 (d, ^1J = 10.0 Hz, 1 H, CH_2OH), 3.75 (d, ^1J = 10.0 Hz, 1 H, CH_2OH), 3.23 (s, 1 H), 2.76 (t, ^1J = 4.0 Hz, 1 H), 2.69 (dd, ^1J = 16.0, 4.0 Hz, 1 H), 2.64–2.54 (m, 1 H), 2.48 (dd, ^1J = 14.0, 3.0 Hz, 1 H), 2.22 (dt, ^1J = 12.5, 2.0 Hz, 1 H), 2.03–1.97 (m, 1 H), 1.95–1.67 (m, 5 H), 1.60–1.30 (m, 16 H with the *tert*-butyl signals superimposed), 0.93 (s, 9 H, *t*Bu), 0.80 (s, 3 H, CH_3), 0.13 (s, 3 H, CH_3), 0.127 ppm (s, 3 H, CH_3). ^{13}C NMR: δ = 220.5 (s), 171.0 (s), 80.8 (s), 72.6 (s), 67.4 (t), 51.6 (d), 51.2 (d), 45.6 (d), 44.7 (t), 43.6 (t), 42.7 (d), 41.8 (t), 34.1 (t), 32.9 (s), 30.5 (t), 28.0 (q), 26.2 (t), 25.8 (q), 21.2 (t), 19.1 (q), 18.2 (s), –5.24 (q), –5.28 ppm (q). MS (CI): *m*/*z* (%) = 481 $[MH]^+$, 407, 349, 274. HRMS: found $[MH]^+$ 481.329651; $C_{27}H_{49}O_5Si$ requires 481.334929.

ARF Reaction of 30: A mixture of protected diol **30** and its hemiketal (0.15 mmol, 72 mg) upon Suarez's ARF reaction afforded, after 3 h, the bicyclic compounds **31** and **32** in 55 and 10% yields, respectively.

Compound 31: ^{1}H NMR: δ = 5.28 (dd, ^1J = 3.5, 2.0 Hz, 1 H, H-2), 3.65 (d, ^1J = 11.5 Hz, 1 H, CH_2OTBDMS), 3.38 (d, ^1J = 11.5 Hz, 1 H, CH_2OTBDMS), 3.30 (dt, ^1J = 8.5, 2.0 Hz, 1 H), 2.98 (dtd, ^1J = 13.5, 5.0, 2.5 Hz, 1 H, H-6), 2.70–2.59 (m, 2 H), 2.29 (dd, ^1J = 17.0, 8.5 Hz, 1 H), 2.07 (dd, ^1J = 15.5, 5.0 Hz, 1 H, H-5), 2.02 (dd, ^1J = 14.0, 2.5 Hz, 1 H, H-7), 1.66 (dd, ^1J = 15.5, 5.0 Hz, 1 H, H-5), 1.68–1.60 (m, 4 H), 1.48 (s, 9 H, *t*Bu), 1.47–1.10 (m, 5 H), 1.05 (s, 3 H, CH_3), 0.86 (s, 9 H, *t*Bu), 0.04 ppm (s, 6 H, 2CH_3). ^{13}C NMR: δ = 178.9 (s), 170.7 (s), 90.0 (s), 81.4 (s), 65.3 (t), 52.4 (d), 46.0 (t), 44.7 (t), 43.4 (t), 40.8 (d), 38.8 (d), 38.5 (d), 38.4 (s), 32.8 (t), 28.0 (q), 27.3 (t), 27.2 (t), 25.7 (q), 20.7 (t), 20.5 (q), 18.2 (s), –5.2 (q), –5.4 ppm (q). MS (CI): *m*/*z* (%) = 607 $[MH]^+$, 492, 423, 365, 245. HRMS: found $[MH]^+$ 607.242599; $C_{27}H_{48}O_5SiI$ requires 607.231581.

Synthesis of the *cis*-Bicyclo[6.4.0]dodecane System 40

Alkylation of *cis*-Methyldecalone 33 with Pentadienoic Ester 1: LDA (5.79 mmol) was formed at 0 °C by addition of BuLi (5.79 mmol, 3.86 mL of a 1.5 M solution) to diisopropylamine (5.79 mmol, 585 mg, 0.80 mL) in THF (3 mL). The LDA solution was cooled to –78 °C and decalone **33** (4.45 mmol, 740 mg) in THF (3 mL)

was injected into it. The reaction mixture was stirred at –78 °C for 0.5 h and warmed to –20 °C. After another 0.5 h, it was again cooled to –78 °C and mesylate **1** (5.34 mmol, 1.4 g) in dry THF (4 mL) was injected into it. The reaction mixture was stirred at –78 °C for 0.5 h, warmed to –30 °C and stirred for 2 h, after which it was quenched with aq. NH_4Cl and extracted with CH_2Cl_2, dried with anhydrous $MgSO_4$, filtered and concentrated. Column chromatography (hexane/ethyl acetate, 9:1) afforded two regioisomers **34** and **35** in a ratio of 1:4 in an overall yield of 61% and their regiochemistry was confirmed by spectroscopic data.

Compound 34: ^{1}H NMR: δ = 7.18 (dd, ^1J = 16.0, 0.5 Hz, 1 H, C*H*=CH–CO_2tBu), 5.83 (d, ^1J = 16.0 Hz, 1 H, CH=C*H*–CO_2tBu), 5.37 (s, 1 H, =CH_2), 5.27 (d, ^1J = 0.5 Hz, 1 H, =CH_2), 2.85 (dd, ^1J = 15.0, 7.5 Hz, 1 H, CH_2CO_2tBu), 2.73–2.61 (m, 1 H), 2.54 (tdt, ^1J = 13.5, 6.5, 0.5 Hz, 1 H), 2.36–2.26 (m, 1 H), 2.16 (dd, ^1J = 15.0, 4.5 Hz, 1 H, CH_2CO_2tBu), 1.96–1.79 (m, 1 H), 1.70–1.40 (m, 17 H with the *tert*-butyl signals superimposed), 1.29–1.10 (m, 2 H), 1.05 ppm (s, 3 H, CH_3). MS (CI): *m*/*z* (%) = 333 $[MH]^+$, 277, 259.

Compound 35: 7.18 (d, ^1J = 16.0 Hz, 1 H, C*H*=CH–CO_2tBu), 5.78 (dd, ^1J = 16.0, 1.5 Hz, 1 H, CH=C*H*–CO_2tBu), 5.39 (s, 1 H, =CH_2), 5.25 (br. s, 1 H, =CH_2), 3.13–2.90 (m, 1 H), 2.89–2.79 (m, 1 H), 2.77–2.53 (m, 2 H), 2.50–2.36 (m, 1 H), 2.31 (dt, ^1J = 5.0, 2.0 Hz, 1 H), 2.28–2.24 (m, 1 H), 2.21–2.06 (m, 3 H), 1.16–1.10 ppm (m, 18 H with the *tert*-butyl and methyl groups superimposed). MS (CI): *m*/*z* (%) = 333 $[MH]^+$, 277, 259.

Intramolecular Michael Addition Reaction of Compound 35: Freshly prepared potassium *tert*-butoxide (2.74 mmol) in *tert*-butyl alcohol (5 mL) was added to a solution of dienyl ketone **35** (2.1 mmol, 700 mg) in THF (5 mL) at 0 °C under argon. After 15 min at 0 °C, the reaction mixture was warmed to room temperature and stirred for 1 h. It was then quenched with aq. NH_4Cl and extracted with CH_2Cl_2, dried with anhydrous $MgSO_4$, filtered and concentrated. Column chromatography (hexane/ethyl acetate, 9:1) afforded only the *endo* isomer **36** in 50% yield. ^{1}H NMR: δ = 5.03 (s, 1 H, =CH_2), 4.90 (s, 1 H, =CH_2), 2.94–2.85 (m, 1 H), 2.61–2.47 (m, 3 H), 2.40–2.20 (m, 3 H), 2.04–1.99 (m, 1 H), 1.85–1.60 (m, 4 H), 1.51–1.00 (m, 15 H with the *tert*-butyl signals superimposed), 0.94 ppm (s, 3 H, CH_3). ^{13}C NMR: δ = 220.4 (s), 170.7 (s), 142.8 (s), 113.1 (t), 80.7 (s), 54.1 (d), 46.8 (d), 45.4 (t), 45.0 (t), 43.9 (d), 42.1 (d), 35.9 (t), 33.5 (s), 30.4 (t), 29.5 (t), 28.0 (q), 26.4 (q), 21.8 (t), 20.5 ppm (t). MS (DCI): *m*/*z* (%) = 333 $[M]^+$, 277, 259. HRMS: found $[MH]^+$ 333.241466; $C_{21}H_{33}O_3$ requires 333.242970.

Dihydroxylation of Compound 36: Following the general procedure, olefin **36** (240 mg, 0.72 mmol) was dihydroxylated to yield an inseparable equilibrium mixture of diol **37** and hemiketal **38** in 79% yield (216 mg). ^{1}H NMR indicated the presence of only trace amounts of hemiketal **38**. ^{1}H NMR of diol **37**: δ = 4.05 (d, ^1J = 10.0 Hz, 1 H, CH_2OH), 3.90 (d, ^1J = 10.0 Hz, 1 H, CH_2OH), 3.30 (br. s, 1 H), 2.90–2.50 (m, 4 H), 2.37–2.10 (m, 2 H), 1.95 (dt, ^1J = 9.0, 1.0 Hz, 1 H), 1.60–1.10 ppm (m, 22 H with the *tert*-butyl and methyl groups superimposed). ^{13}C NMR: δ = 221.8 (s), 172.4 (s), 81.3 (s), 72.8 (s), 66.1 (t), 51.8 (d), 51.6 (d), 44.4 (t), 43.6 (t), 42.2 (d), 41.6 (d), 34.1 (t), 33.9 (t), 30.7 (s), 30.1 (t), 27.9 (q), 26.6 (q), 21.7 (t), 19.6 ppm (t). MS (CI): *m*/*z* (%) = 367 $[MH]^+$, 293, 275, 257. HRMS: found $[MH]^+$ 367.250370; $C_{21}H_{35}O_5$ requires 367.248450.

***tert*-Butyldimethylsilylation of Diol 37:** Diol **37** (containing a trace amount of hemiketal **38**; 0.50 mmol, 183 mg) on reaction with imidazole (1.1 mmol, 75 mg) and TBDMSCl (0.75 mmol, 113 mg) in dry DMF (2 mL) yielded the monosilyl ether **39** in 74% yield. ^{1}H NMR: δ = 4.20 (d, ^1J = 10.0 Hz, 1 H, CH_2OTBDMS), 3.72 (dd, ^1J = 10.0, 1.5 Hz, 1 H, CH_2OTBDMS), 3.16 (s, 1 H), 2.77–2.66 (m, 2 H), 2.58–2.46 (m, 2 H), 2.26–2.15 (m, 2 H), 2.13–2.07 (m, 1 H), 1.93 (dd, ^1J = 15.0, 2.5 Hz, 1 H, CH_2CO_2tBu), 1.86–1.64 (m, 4 H), 1.60–1.30 (m, 15 H with the *tert*-butyl signals superimposed), 1.04 (s, 3 H, CH_3), 0.94 (s, 9 H, *t*Bu), 0.144 (s, 3 H, CH_3), 0.136 ppm (s, 3 H, CH_3). ^{13}C NMR: δ = 220.7 (s), 171.1 (s), 80.7 (s), 72.3 (s), 66.3 (t), 50.8 (d), 50.5 (d), 43.9 (t), 43.3 (t), 42.3 (d), 42.1 (d), 34.3 (t), 33.5 (t), 30.7 (s), 30.0 (t), 27.9 (q), 26.8 (q), 25.8 (q), 21.7 (t), 19.7 (t), 18.1 (s), –5.2 (q), –5.3 ppm (q). MS (CI): *m*/*z* (%) = 481 $[MH]^+$, 407, 346, 275. HRMS: found $[MH]^+$ 481.339000; $C_{27}H_{49}O_5Si$ requires 481.334929.

ARF Reaction of 39: Protected diol **39** and trace amounts of its hemiketal (0.202 mmol, 97 mg) upon Suarez's ARF reaction afforded, after 2 h, the bicyclic compound **40** as a single stereo- and regioisomer in 13% yield along with 21% of tricyclic diketone **41**. Compound **40**: ^{1}H NMR: δ = 5.13 (dd, ^1J = 4.5, 2.0 Hz, 1 H, H-2), 3.63 (d, ^1J = 10.5 Hz, 1 H, CH_2OTBDMS), 3.39 (d, ^1J = 10.5 Hz, 1 H, CH_2OTBDMS), 3.23 (dt, ^1J = 8.5, 1.5 Hz, 1 H), 2.98–2.86 (m, 1 H), 2.58 (dd, ^1J = 17.0, 1.5 Hz, 1 H, CH_2CO_2tBu), 2.47 (dd, ^1J = 17.0, 8.5 Hz, 1 H, CH_2CO_2tBu), 2.30–2.10 (m, 2 H), 2.02–1.65 (m, 6 H), 1.45 (s, 9 H, *t*Bu), 1.31–1.08 (m, 8 H with the methyl signals superimposed), 0.85 (s, 9 H, *t*Bu), 0.04 (s, 3 H, CH_3), 0.03 ppm (s, 3 H, CH_3). MS (DCI): *m*/*z* (%) = 607 $[MH]^+$, 551, 492, 423, 365, 291. HRMS: found $[MH]^+$ 607.227782; $C_{27}H_{47}O_5SiI$ requires 607.231581.

Compound 41: ^{1}H NMR: δ = 3.29 (ddd, ^1J = 7.0, 6.0, 4.0 Hz, 1 H), 2.86–2.73 (m, 3 H), 2.57–2.46 (m, 2 H), 2.12 (dd, ^1J = 16.5, 6.0 Hz, 1 H), 2.03–1.92 (m, 1 H), 1.80–1.60 (m, 3 H), 1.44 (s, 9 H), 1.42–0.96 (m, 7 H), 0.95 ppm (s, 3 H). ^{13}C NMR: δ = 216.8 (s), 206.2 (s), 170.4 (s), 81.0 (s), 53.0 (d), 49.7 (t), 46.0 (t), 43.4 (d), 43.1 (d), 32.8 (d), 32.6 (t), 30.2 (s), 29.3 (t), 28.0 (q), 26.6 (q), 25.8 (t), 21.4 (t), 19.9 ppm (t). MS (DCI): *m*/*z* (%) = 335 $[MH]^+$, 319, 207. HRMS: found $[MH]^+$ 335.229000; $C_{20}H_{31}O_4$ requires 335.222235.

Synthesis of Diquinane 43: LDA (0.27 mmol) was formed at 0 °C by addition of BuLi (0.27 mmol, 0.18 mL of a 1.5 M solution in THF) to diisopropylamine (0.27 mol, 27 mg, 0.037 mL) in THF (92 mL) under argon. The solution was then cooled to –78 °C. Iodolactone **16** (64 mg, 0.12 mmol) dissolved in THF (1 mL) was added to the LDA and the reaction mixture was stirred for 0.5 h. The mixture was quenched with aq. NH_4Cl and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water, dried with anhydrous $MgSO_4$, filtered and concentrated. Recrystallization in petroleum ether afforded the diquinane **43** in 78% yield (38 mg). M.p. 101 °C. ^{1}H NMR: δ = 3.88 (d, ^1J = 11.5 Hz, 1 H, CH_2OTBDMS), 3.82 (d, ^1J = 11.5 Hz, 1 H, CH_2OTBDMS), 2.73 (ddd, ^1J = 10.5, 9.5, 5.0 Hz, 1 H, H-5), 2.62 (dd, ^1J = 14.5, 5.0 Hz, 1 H, CH_2CO_2tBu), 2.46 (ddd, ^1J = 10.5, 8.0, 6.0 Hz, 1 H, H-6), 2.20 (dd, ^1J = 14.5, 9.5 Hz, 1 H, CH_2CO_2tBu), 2.17–2.10 (m, 1 H), 2.02–1.86 (m, 2 H), 1.82–1.60 (m, 4 H), 1.50–1.40 (m, 10 H with the *tert*-butyl signals superimposed), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H). ^{13}C NMR: δ = 178.4 (s), 170.8 (s), 94.0 (s), 80.8 (s), 61.7 (t), 59.5 (s), 49.2 (d), 40.9 (d), 40.2 (t), 35.0 (t), 28.0 (q), 26.7 (t), 26.2 (t), 25.7 (q), 22.6 (t), 18.2 (s), –5.3 (q), –5.4 ppm (q). MS (DCI): *m*/*z* (%) = 355 $[MH – 56]^+$, 297, 157. HRMS: found $[MH – 56]^+$ (McLafferty cleavage) 355.186503; $C_{18}H_{31}O_5Si$ requires 355.194078.

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