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# Face selectivity in the reactions of 2,4-disubstituted adamantanes and their modification by inclusion in β-cyclodextrin solutions

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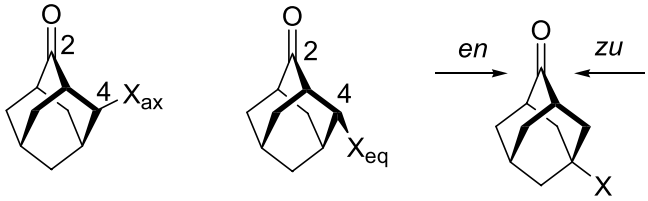
**Abstract**—Sodium borohydride reduction reactions on 4-X-adamantan-2-ones (where X=ethyleneketal **11**, ethylenethioketal **12**, and methylene **15**) were studied, which gave *Z*-alcohols **16** and **17** (from *en*-face attack) as the predominant products for ketones **11** and **12**, but gave 1:1 mixture of *Z*- and *E*-**18** alcohols for ketone **15**. The *en*/*zu* face selectivity of **15** in sodium borohydride reduction was enhanced to 32/68 in β-CD solution. Both 1,3-dipolar addition and dichlorocarbene addition reactions on 4-ethyleneketal-2-methyleneadamantane **13** underwent again predominant *en*-face attack to give products in an *E*/*Z* ratio of >99:1 and 92:8, respectively. The exceptional high *zu*-face selectivity on the dichlorocarbene addition reaction of **15** may be explained by a temporal complexation between the carbene and the $C_4$-oxo group. In the epoxidation reaction of **13** and **15** the *zu*-face attack products were favored despite their steric congestions suggesting that hydrogen bonding interaction between the peroxide reagent and the $C_4$-oxo or 4-ethyleneketal is involved.


## 1. Introduction

Many experimental probes have been devised to identify the various steric and electronic factors that influence π-facial selectivity in nucleophilic, electrophilic, and cycloaddition reactions, among them, sterically unbiased systems offer intrinsic advantage in isolating and evaluating electronic effects.[1–4] Relatively fewer studies have been reported on the reactions of 4-substituted adamantan-2-ones **1**- and **2**-**X** comparing to the very popular and more thoroughly studied 5-substituted adamantan-2-ones **3**-**X**. One barrier for using 4-substituted-adamantan-2-ones **1**- and **2**–**X** is the multi-step syntheses involved in the preparation of these probes. Furthermore, an axial (but not equatorial) 4-substituent is expected to have a strong steric influence on the chemical reactivity of a nearby trigonal center; rendered it difficult in studying pure electronic effects. Despite the difficulties involved, there are some scattered reports[5,6] on the face selectivity of 4-substituted adamantanes.




**1-X** **2-X** **3-X**

The steric effect of an axial substituent makes itself felt with even the smallest fluoro substituent: sodium borohydride attacks **1**-**F** exclusively at the *en* face to give the pure diaxial alcohol **4**-**F**. Similar data were found for the reduction of **1**-**Br**.[5,6] An equatorial fluoro substituent in **2**-**F**, however, give the diequatorial alcohol **5**-**F** and isomer **6**-**F** in a ratio of 67:33 which resembles the face selectivity in **3**-**F**.[1a] In the sodium borohydride reduction of **7**, adamantan-2-one with two equatorial β-bromosubstituents, a higher face selectivity was found (**8**:**9**=86:14) and the results were reconciled with Cieplak's model (see Chart 1).[1a,5]

Adamantane derivatives have received considerable attention because of their diverse biological activity;[7] especially when substituted with spiro-cyclopropane or spiro-pyrrolidine groups, they are known to have antiviral activity.[7c] We report here facile syntheses of some 2,4-disubstituted adamantanes **11**–**15** and face selectivity studies on these probes that yielded various spiro acetals, cyclopropanes, oxiranes, and isoxazolines. Despite the difficulties in

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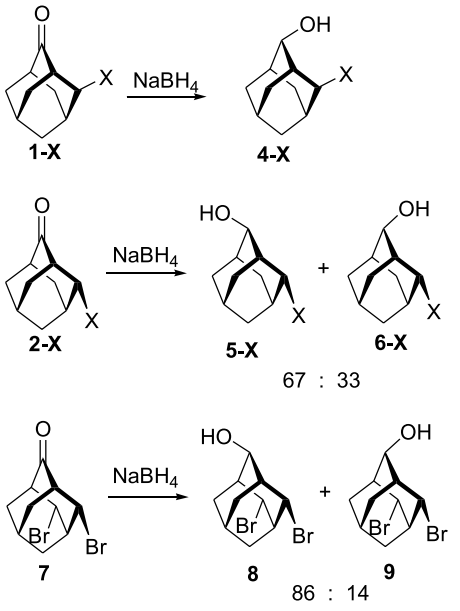
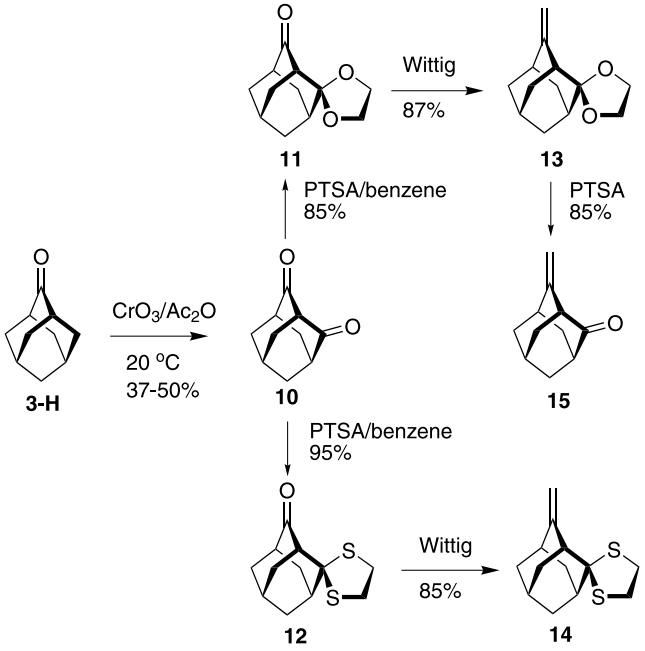



**Chart 1.**

dissecting electronic effects from these sterically biased probes, we found evidences to support 'neighboring group participation' in some of the reactions, furthermore, an unexpected *syn*-face enhancement in sodium borohydride reduction reactions of a **15**·β-CD complex is observed.

## 2. Results and discussion

Adamantane-2,4-dione **10** was first synthesized by Wynberg[8] in 1968 and latter by McKervey[9] and Duddeck[10] all through multiple-step syntheses. In 1985 Gilbert reported[11a] a direct oxidation of adamantan-2-one **3-H** by $CrO_3$ in acetic anhydride gave **10** in 20% yield. We followed the procedures by Gilbert and obtained a good yield (typical yields are in 37–50% range) of **10**.[11b] Compounds **11** and **12** were prepared through the protection of carbonyl group by ethylene glycol and 1,2-ethanedithiol, respectively. Compounds **13** and **14** were prepared in high yields by the Wittig reaction of **11** and **12**, respectively. The acid catalyzed deprotection of **13** gave **15** in 85% yield. The synthetic pathways are outlined in Scheme 1.



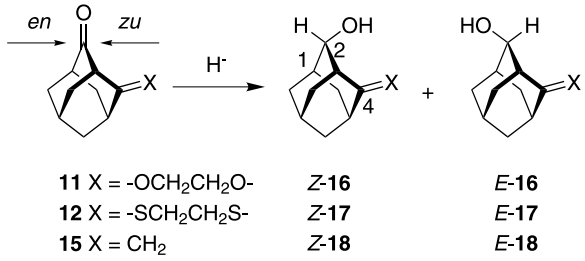

**Scheme 1.**

Sodium borohydride (or LAH) reduction of 4-ketaladamantan-2-one **11** or 4-thioketal-adamantan-2-one **12**, through *en*-face attack by hydride, gave *Z*-alcohols (*Z*-**16** or *Z*-**17**) as the only products. On the other hand, the reduction of 4-methyleneadamantan-2-one **15** gave *Z*- and *E*-**18** alcohols as a 1:1 mixture (Scheme 2 and Table 1). The reduction of **11** that led to *Z*-**16** as the only product has been reported in literature.[12a] Similarly, the major reduction product of thioketal-**12** is expected to be *Z*-**17** due to severe steric hindrance caused by the 4-thioketal group. The configuration of the reduction products *Z*- and *E*-**18** can be easily judged from their $^1$H NMR spectra where the 4-methyleneprotons show two doublets (AB pattern) in *Z*-**18** but a singlet in *E*-**18** due to the magnetic anisotropy effect exerted by the 2-hydroxy group. Furthermore, the structure of *Z*-**18** can be independently synthesized from the acid-catalyzed deprotection of *Z*-**16** to *Z*-**19** followed by a Wittig reaction[12b] to give *Z*-**18** exclusively (see Scheme 3). Thus, 4-methylene group seems to play no effect on the reduction

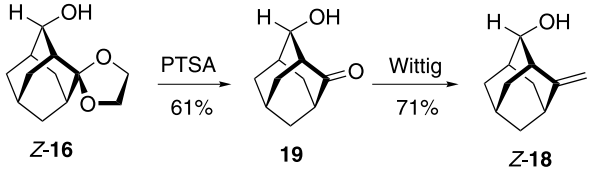
**Table 1.** Sodium borohydride and lithium aluminum hydride reduction reactions of 4-substituted-adamantan-2-ones **11**, **12**, and **15**

| Compound | Reaction conditions[a] | *Z*/*E* ratios[b] | Isolated yield, % |
|---|---|---|---|
| **11** | $NaBH_4$/MeOH | **16** (>99:1) 98 | 98 |
| **11** | $LiAlH_4$/THF | **16** (>99:1) | 70[c] |
| **12** | $NaBH_4$/MeOH | **17** (>99:1) | 98 |
| **12** | $LiAlH_4$/THF | **17** (>99:1) | 71 |
| **15** | $NaBH_4$/MeOH | **18** (51:49) | 98 |
| **15** | $LiAlH_4$/THF | **18** (49:51) | 73 |

[a] Reaction was carried out at 25 °C for 1 h.
[b] Note that *en* attack of hydride leads to *Z*-alcohol. Product ratios were analyzed by GC and the error bars were estimated to be ±2%.
[c] Data is consistent with that reported in Ref. 12a.




**Scheme 2.**




**Scheme 3.**

of 4-methylene-adamantan-2-one **15**. Similar results have been reported by Duddeck[10c] where *tert*-butyllithium addition of **15** gave a 1:1 mixture of *E*- and *Z*-alcohols. To our delight, the face selectivity on the reduction of **15** can be altered by inclusion of itself into β-CD cavity, but the results are opposite to our expectation based on previous model of **3-X** in β-CD[13a] (vide infra).

The 50/50 *en*/*zu* face selectivity of the sodium borohydride reduction of **15** in THF or methanol becomes 45/55 in water. The effect of β-CD complexation on the *en*/*zu* selectivity of **15** in sodium borohydride reduction is shown in Figure 1, which reaches a maximum value of 32/68 at 15 mM of β-CD. The yields of *Z*- and *E*-**18** alcohols from these reactions were in the range of 75–82% when β-CD was below 3 mM, but slightly decreased to 70–73% when β-CD concentration was above 6 mM. The product ratio varies with the concentration of β-CD in the way expected from the fact that saturation will be approached if the concentration of β-CD is made sufficiently high.[13,14] Based on the binding constants (260 $M^{-1}$) of **15** with β-CD (vide infra) and assuming a 1:1 complex, one can calculate the percentage of compound **15** bound by β-CD to be 75% if the starting concentration of **15** is 5 mM and β-CD is 15 mM. Accordingly, after correcting for the unbound **15** the theoretical value of *en*/*zu* face selectivity in the reduction of **15**·β-CD should be 22:78 instead of the observed 32:68. The enhanced *zu*-face attack in **15**·β-CD complex is surprising because one would have expected the opposite had its conformation been similar to that of the reported **3-X**·β-CD.[13a] In order to gain some insights on the structures of **15**·β-CD complexes, both $^1$H NMR titration experiments and molecular dynamic calculations were carried out (see Supporting Information).

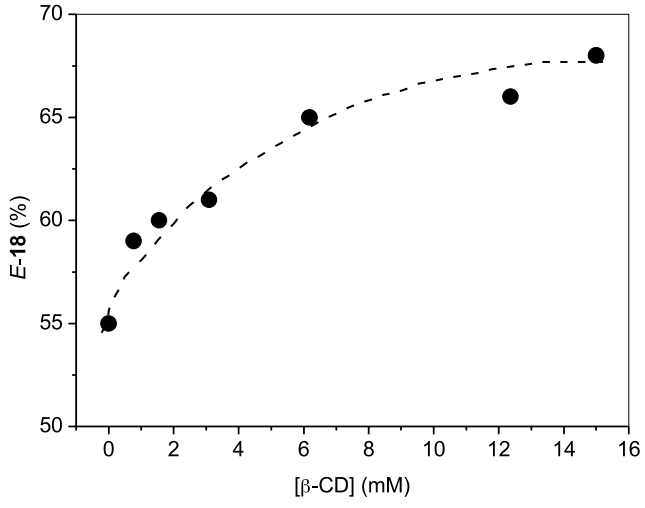



**Figure 1.** The percentage *E*-**18** product obtained in the sodium borohydride reduction reactions of **15** (5 mM) in aqueous solution as a function of added β-CD.

Evidences for complexation of **15** by β-CD were obtained from $^1$H NMR spectra, which show that $H_3$ ($\Delta\delta = -0.055$ ppm) and $H_5$ ($\Delta\delta = -0.087$ ppm) of β-CD (which are oriented toward the interior of the CD cavity) are shifted upfield considerably in the presence of **15**. By contrast, $H_1$, $H_2$, and $H_4$, all located on the exterior wall of CD, either have small downfield shifts or are unaffected (Fig. 2).[15] On the other hand, the $H_{1'}$, $H_{3'}$, and $H_{5'}$ of 4-methyleneadamantan-2-one **15** are substantially downfield shifted in the presence of β-CD and their chemical shift difference $\Delta\delta$ is: +0.18, +0.11, and +0.13 ppm, respectively (Fig. 3).[15] These observations are consistent with the notion that a complex is formed between β-CD and **15** and they most likely have 1:1 stoichiometric ratio, similar to those of adamantane derivatives found in several X-ray crystallography data.[16] The binding constant for complexes of **15** with β-CD was determined to be $260 \pm 20\ M^{-1}$ by Benesi–Hilderbrand plot (Figs. S-1 and S-2),[14,17] where the reciprocal chemical shift differences of guest **15** are plotted with the reciprocal concentration of β-CD.

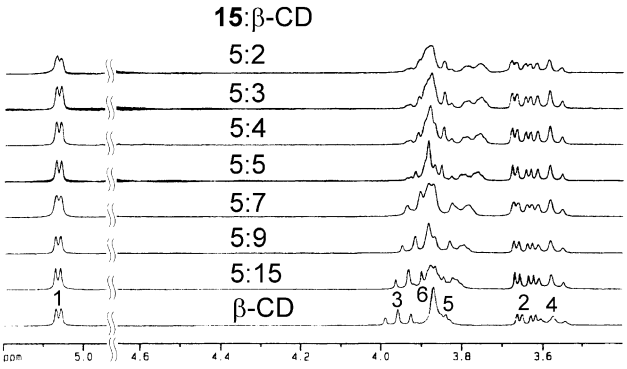



**Figure 2.** Effects of **15** on the $^1$H NMR spectra of β-CD in $D_2O$; where the concentration of **15** was fixed at 5 mM but the concentration of β-CD decreased gradually from bottom (15 mM) to top (2 mM). Spectra were measured at 300 K.

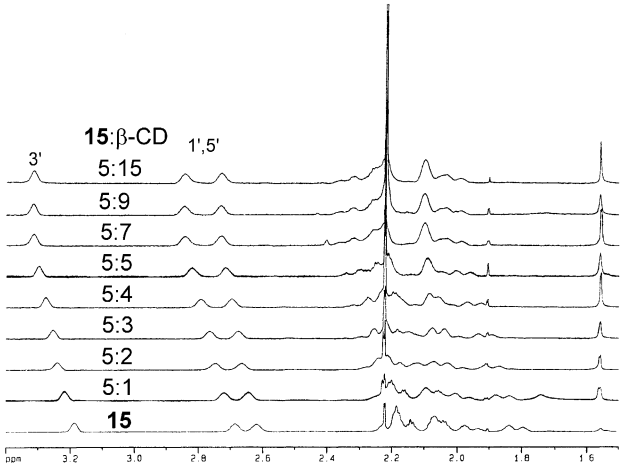



**Figure 3.** Effects of β-CD on the $^1$H NMR spectra of **15** (5 mM) in $D_2O$ solution; where the concentrations of β-CD increases gradually from bottom (0 mM) to top (15 mM). The signals of protons on the $C_4$-methylidene of **15** were buried in the huge water peak and were omitted. Spectra were measured at 300 K.

Four of the most likely conformations of **15** in β-CD are shown in Chart 2 and they are complexes **A**–**D**. The results of sodium borohydride reduction reactions on the complex of **15** in β-CD is out of our expectation, because if complexes **C** and **D** are the major conformations (similar to those reported for 5-substituted-adamantan-2-ones **3-X**·β-CD)[13a] one would expect that predominant *Z*-alcohol **18** be

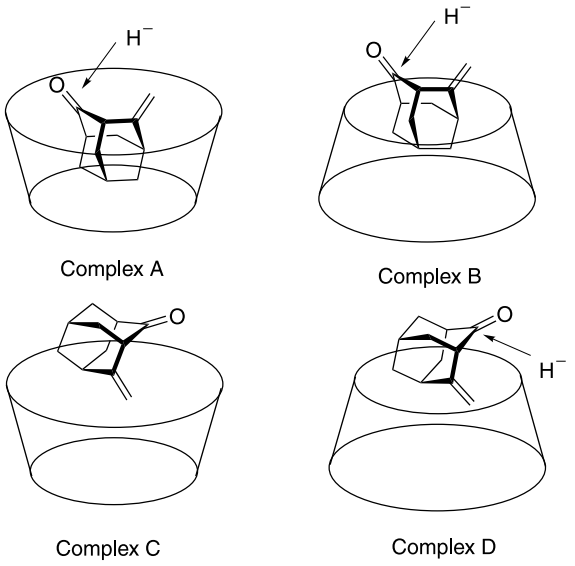
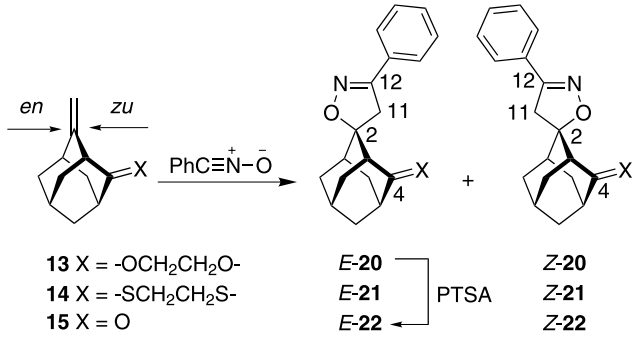



**Chart 2.**

formed. On the contrary, *E*-alcohol **18** became the major product when 3 equiv. of β-CD vs. **15** was used. Alternatively, if complexes **A** and **B** are the major conformations of the **15**·β-CD complexes, one may easily explain why more *E*-**18** was formed at high [β-CD] because the torus of β-CD protects the *en*-face of **15** from hydride attacks. Theoretical calculations were thus carried out to gain more insight about the conformations of **15**·β-CD complexes.

Snapshots from the MD simulations showed that preferred complexes are **C** and **D**, both with the hydrophobic methylidene groups pointing towards the CD cavity. The results are in accord with the previous proposed model **3-X**·β-CD, where a dramatic reversal in face selectivity was achieved by partial blockage of the π-face *zu* to the bulky 5-substituent of a **3-X**·β-CD complex by the CD host.[13a] Thus, the results from the simulations would predict the reduction reaction to yield the *Z*-**18** alcohol as the dominant product by partial blockage of the *zu*-face of **15** from hydride attack. Yet, the predominant formation of the *E*-**18** may indicate that β-CD has mediated the reaction through hydrogen bonding interaction of its hydroxyl groups with the metal hydride; it therefore favors a *zu*-face attack.[17b]

The 1,3-dipolar cycloaddition reactions of the 4-substituted-2-methyleneadamantane **13**–**15** with benzonitrile oxide




**Scheme 4.**

were studied next (Scheme 4).[18] Only *E*-isoxazolines **20** and **21** were formed in the reaction of **13** and **14**, whereas, a 1:1 mixture of *E*- and *Z*-isoxazolines **22** were obtained in the reaction of **15** (Table 2). The *E*-adducts **20** and **21** were obtained from the expected attack of benzonitrile oxide on the less-hindered side, namely, the *en*-face that is opposite to the 4-X substituents. The face selectivity in the 1,3-dipolar reactions of **13** and **14** is similar to that of reduction in **11** and **12**, but the reaction of **14** gave a very poor yield of product. Most of the starting material **14** could be recovered from the 1,3-dipolar reaction due to its poor reactivity.

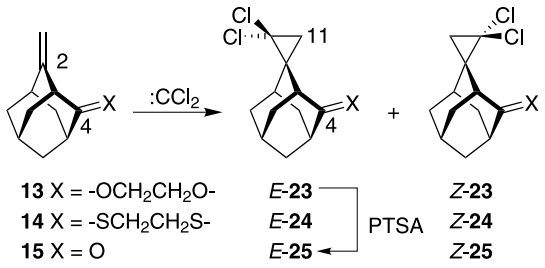
**Table 2.** Product ratios and yields in the 1,3-dipolar addition, carbene addition, and *m*CPBA epoxidation reactions of 4-substituted-2-methyleneadamantanes **13**–**15**

| Substrate | *E*/*Z* product ratio[a] (yield, %) | | |
|---|---|---|---|
| | 1,3-Dipolar addition | Dichlorocarbene addition | *m*CPBA epoxidation |
| **13** | *E*-**20**:*Z*-**20** >99:1 (49%) | *E*-**23**:*Z*-**23** 92:8 (98%) | *E*-**26**:*Z*-**26** 49:51 (80%) |
| **14** | *E*-**21**:*Z*-**21** >99:1 (trace) | *E*-**24**:*Z*-**24** No reaction | *E*-**27**:*Z*-**27** Complex mixture |
| **15** | *E*-**22**:*Z*-**22** 49:51 (51%) | *E*-**25**:*Z*-**25** 1:>99[b] (48%) | *E*-**28**:*Z*-**28** 33:67[b] (71%) |

[a] Product ratios determined by $^1$H NMR spectroscopy with an estimated error of ±5% unless otherwise specified. Note that in the three types of reactions, *en* attack of reagents leads to *E*-products.
[b] Ratios determined by GC with an estimated error of ±2%.

The *E* and *Z* configuration of isoxazolines **20** and **21** are assigned by inspecting the splitting patterns of the methylene protons on $C_{11}$, in which a larger chemical shift difference $\Delta\nu_{AB}$ is expected for the *E*-isomer than for the *Z*-isomer due to their closer interaction with 4-ketal or 4-thioketal groups. For example, the $\Delta\nu_{AB}$ of the methylene protons on $C_{11}$ of *E*-**21** was found to be 0.62 ppm but was 0.26 ppm for the *Z*-**21**. The assignments of *E*- and *Z*-**22** were further confirmed by an independent synthesis of *E*-**22** through PTSA catalyzed conversion of *E*-**20** to *E*-**22**. Lightner et al. reported[12a] that the magnetic anisotropy of the $C_4$-oxo group can deshield the $C_{11}$ carbon in a very similar structure and our observations are consistent with their statements; for example, the chemical shift of $C_{11}$ is 43.6 ppm as an axial substituent (*E*-**22**) but is 43.0 ppm as an equatorial one (*Z*-**22**). The 1:1 face selectivity of **15** by nitrile oxide is unexpected if one considers the $C_4$-oxo to be an electron-withdrawing group, where the Cieplak's model[19] would have predicted a favored *Z*-**22** product (from *zu*-face attack). On the other hand, an electrostatic repulsion between the nitrile oxide and the $C_4$-oxo group of **15** should disfavor a *zu*-face attack, thus counter-balanced the face preference by hyperconjugative effect. The photoreactions of **15** with acetone and benzophenone were reported by Mlinarić–Majerski[20a] to give *E*-oxetanes (from *en*-face attack) as the major product (in 70:30 ratios); where, both steric effect and the electronic effect of $C_4$-oxo group were used to rationalize the observed products.

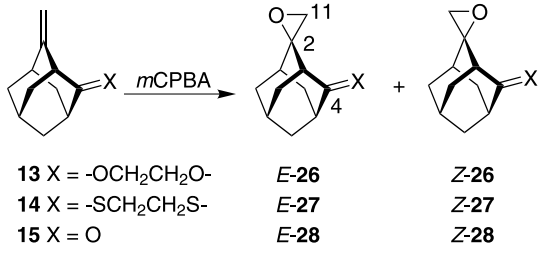
The electrophilic addition reactions of dichlorocarbene on 4-substituted-2-methylene-adamantanes **13**–**15** were carried out next (Scheme 5 and Table 2). The addition of




**Scheme 5.**

dichlorocarbene with **13** gave *E*- and *Z*-spirocyclopropanes **23** in 98% yield, in a ratio of 92:8 (determined by $^1$H NMR analysis). However, no reaction was found when **14** replaced **13** in a similar reaction conditions for carbene additions. To our surprise, the addition of dichlorocarbene with 4-methylene-2-adamantanone **15** gave *Z*-spirocyclopropanes **25** as the predominant product (based on GC analysis, *E*/*Z*-**25**=1:>99) in 48% isolated yield. The configuration assignment of *E*- and *Z*-spirocyclopropanes **23**–**25** can again be judged from the splitting pattern of the methylene protons of $C_{11}$ on the spirocyclopropanes, in which a larger chemical shift difference $\Delta\nu_{AB}$ is expected for the *E*-isomer than the *Z*-isomer due to their closer interaction with 4-ketal or 4-thioketal groups. Furthermore, the structure of *E*-**25** can be independently synthesized from the acid catalyzed deprotection of *E*-**23**. The exclusive formation of *Z*-**25** reminds us about the Simmons–Smith reaction of homoallylic 4-cyclohexenols[21] which gave specifically *syn* cyclopropane product. The results imply that the $C_4$-oxo group of **15** may have directed the dichlorocarbene to the *zu*-face; therefore, leads to high yield of *Z*-**25**.

In all reactions carried out on **13**, the *en*-face attack had almost always been the predominant one; we were therefore a bit surprised to find that the epoxidation of **13** by *m*CPBA gave *E*- and *Z*-oxiranes **26** as a 1:1 mixture (Scheme 6). Moreover, complex mixtures were obtained in the epoxidation of **14** presumably due to the attack of *m*CPBA on the sulfur atoms of sulfide, because the 2-methylene group was found to be intact by $^1$H NMR analysis. For comparison, the epoxidation of **15** gave *E*- and *Z*-oxiranes **28** (33:67) in 71% yield (Table 2). The somewhat high *zu*-face reactivity on **13** and **15** despite their steric congestions, suggests that hydrogen-bonding interaction between the *m*CPBA and $C_4$-oxo or ketal groups is quite likely. Remember that the hydroxyl group of an allylic alcohol is well-known to direct *m*CPBA in a highly stereoselective *syn* epoxidation reaction,[22] here, the $C_4$-oxo seems to play a similar role. It is worth noting that the *zu*-face epoxidation is more favored




**Scheme 6.**

on **15** than on **13** and we believe that the results are consistent with the Cieplak's model.[19] In other words, since $C_4$-oxo is considered to be stronger electron-withdrawing than the ethylene ketal group, therefore, the reaction on C=C double bond of **15** (or **13**) is expected to occur preferentially from a direction anti to the more electron-rich C–C bonds.

The configuration of *E*- and *Z*-**26** was judged from the $^1$H NMR spectrum of the ketal group, where the splitting pattern of *Z*-**26** is more complex than *E*-**26** due to its close interaction with oxirane. On the other hand, the configuration assignments of *E*- and *Z*-**28** can also be judged from the splitting pattern of the methylene protons (of $C_{11}$) of the oxirans, in which a larger chemical shift difference $\Delta\nu_{AB}$ is expected for the *E*-isomer (0.11 ppm) than for the *Z*-isomer (0.08 ppm) due to their closer interaction with $C_4$-oxo group. Furthermore, the protons on $C_{11}$ are more downfield for the *E*-**28** than those for the *Z*-**28** due to their interactions with $C_4$-oxo. Independent syntheses of *E*- and *Z*-**28** from acid-catalyzed deprotection of **26** with PTSA were unsuccessful because the oxirane rings tend to be opened by the acid too.

## 3. Conclusion

The results studied here indicate that in the reduction and 1,3-dipolar addition reactions of 4-disubstituted-2-adamantylidene or adamantan-2-one **11**–**14** steric hindrance is the dominating factor in determining the face selectivity. Despite the difficulties in isolating electronic effects from these steric biased probes, we found valuable information about 'neighboring group participation' in the carbene addition and epoxidation reactions. Finally, an enhanced *zu*-face attack of hydride on **15** can be achieved by complexation with β-CD which is opposite to our expectation based on previously proposed model.[13a,17b] Molecular dynamic calculations as well as $^1$H NMR titration experiments support the 1:1 inclusion complexes of **15** with β-CD.

## 4. Experimental

### 4.1. General

**4.1.1. The preparation of adamantane-2,4-dione (10).**[11a,b] To a chromium oxide solution (66.7 g, 0.67 mol) in acetic anhydride (300 mL) was added dropwise a solution of 2-admantanone (**3**-**H**) (16.7 g in 200 mL of acetic anhydride) through addition funnel under nitrogen. The solution was vigorously stirred and the temperature was controlled at 20 °C by a circulator. After ten days, the solution was neutralized with saturated sodium bicarbonate solution and extracted several times (100 mL×6) with methylene chloride. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. The mixture was recrystallized in *n*-hexane/ethyl acetate (5/1) to give **10** (5.5 g, 33.5 mmol) and the residue from recrystallization was purified on a silica gel column by elution with *n*-hexane/ethyl acetate to give **10** (3.3 g, 20.1 mmol). The total amount of **10** is 8.8 g (an average of 37–50%).

Colorless solid; mp 279–281 °C (lit.[8] 280–282 °C, lit.[10a] 282–283 °C); $\delta_H$ 1.75–1.80 (m, 1H), 1.99–2.18 (m, 6H), 2.41 (bs, 2H), 2.77 (bs, 2H), 3.38 (bs, 1H); $\delta_C$ 27.0 (CH), 30.1 ($CH_2$), 38.3 ($CH_2$), 44.2 ($CH_2$), 45.2 (CH), 68.4 (CH), 208.6 (Cq); MS (EI, *m/z*) 164 ($M^+$, 28), 95 (40), 79 (100), 66 (50), 55 (59), 53 (39); HRMS *m/z* calcd for $C_{10}H_{12}O_2$ 164.0838, found 164.0830. The preparation of 4-ethyleneketaladamantan-2-one (**11**) followed a literature procedure.[5]

**4.1.2. Synthesis of 4-ethylenethioketaladamantan-2-one (12).**[20b] The procedure for the synthesis of **12** is similar to that of **11**, and the amount of reagents used is as follows: **10** (104 mg, 0.63 mmol), ethane-1,2-dithiol (64 mg, 0.68 mmol), PTSA·$H_2O$ (30 mg, 0.16 mmol) and benzene (6 mL). The yield is 95%. Colorless liquid; (lit.[20b] mp 56–59 °C); $\delta_H$ 1.89–2.00 (m, 6H), 2.15–2.19 (m, 3H), 2.37–2.45 (m, 2H), 2.64 (bs, 1H), 3.18–3.24 (m, 4H); $\delta_C$ 25.7 (CH), 36.1 ($CH_2$), 36.6 ($CH_2$), 38.4 ($CH_2$), 38.7 ($CH_2$), 39.2 ($CH_2$), 39.4 ($CH_2$), 40.7 (CH), 45.0 (CH), 60.8 (CH), 76.3 (Cq), 213.9 (Cq); MS (EI, *m/z*) 240 ($M^+$, 100), 212 (78), 184 (34); HRMS *m/z* calcd for $C_{12}H_{16}OS_2$ 240.0644, found 240.0651.

**4.1.3. Synthesis of 4-ethyleneketal-2-methyleneadamantane (13).** To a solution of methyltriphenylphosphonium bromide (941 mg, 2.51 mmol) in dried tetrahydrofuran (10 mL) at 0 °C was slowly added *n*-butyllithium (2.5 M in *n*-hexane, 2.50 mmol) via syringe under nitrogen. After the solution was stirred for 1–2 h at room temperature, **11** (253 mg, 1.21 mmol) in dried tetrahydrofuran (10 mL) was added gradually and refluxed for 24 h. After cooling, the solution was washed with water and separated into organic and water layers. The water layer was extracted several times (30 mL×4) with methylene chloride. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified on a silica gel column by elution with *n*-hexane/ethyl acetate to give **13** (217 mg, 87%). Colorless liquid; $\delta_H$ 1.72–2.18 (m, 10H), 2.41 (m, 2H), 3.94–3.98 (m, 4H), 4.61, 4.66 (AX, $J$= 1.8 Hz, 2H); $\delta_C$ 26.8 (CH), 34.3 ($CH_2$), 35.0 ($CH_2$), 36.0 (CH), 37.1 ($CH_2$), 37.6 (CH), 39.0 ($CH_2$), 47.5 (CH), 64.2 (2×$CH_2$), 103.7 ($CH_2$), 111.2 (Cq), 154.5 (Cq); MS (EI, *m/z*) 206 ($M^+$, 100), 91 (32), 73 (47), 57 (36); HRMS *m/z* calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1297.

**4.1.4. Synthesis of 4-ethylenethioketal-2-methyleneadamantane (14).** The procedure for the synthesis of **14** is similar to that of **13**. The amount of reagents used is as follows: **12** (900 mg, 3.75 mmol), methyltriphenylphosphonium bromide (2.19 g, 5.77 mmol), dried tetrahydrofuran (100 mL) and *n*-butyllithium (2.5 M in *n*-hexane, 5.63 mmol). The yield is 85%. Colorless solid; mp 51–52 °C; $\delta_H$ 1.69–1.84 (m, 6H), 2.01 (bs, 1H), 2.14–2.26 (m, 3H), 2.40 (bs, 1H), 2.58 (bs, 1H), 3.14–3.24 (m, 4H), 4.60, 4.62 (AB, $J$=2.2 Hz, 2H); $\delta_C$ 26.4 (CH), 35.9 ($CH_2$), 37.1 (CH), 38.2 ($CH_2$), 38.5 ($CH_2$), 39.1 ($CH_2$), 39.3 ($CH_2$), 39.4 ($CH_2$), 41.9 (CH), 52.6 (CH), 77.6 (Cq), 104.7 ($CH_2$), 154.3 (Cq); MS (EI, *m/z*) 238 ($M^+$, 27), 210 (32), 185 (49), 183 (100), 108 (59); HRMS *m/z* calcd for $C_{13}H_{18}S_2$ 238.0851, found 238.0854. Anal. calcd for $C_{13}H_{18}S_2$: C, 65.49; H, 7.61, found: C, 65.38; H, 7.66.

**4.1.5. Synthesis of 4-methyleneadamantan-2-one (15).** A well-stirred solution of **13** (755 mg, 3.70 mmol) in 70% acetone (aq) (20 mL) was added PTSA·$H_2O$ (84.5 mg, 0.44 mmol) as a catalyst and maintained at 35 °C for 22 h. The solution was washed with water and separated into two layers. The water layer was extracted several times (5 mL× 4) with methylene chloride. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified on a silica gel column by elution with *n*-hexane/ethyl acetate to give **15** (566 mg, 85%). Colorless solid; mp 280–281 °C (lit.[23] 135–138 °C; lit.[24] 280–282 °C); $\delta_H$ 1.88–2.12 (m, 9H), 2.59–2.62 (m, 2H), 3.14 (bs, 1H), 4.62, 4.66 (AB, $J$=15 Hz, 2H); $\delta_C$ 27.5 (CH), 37.6 (CH), 37.6 ($CH_2$), 37.9 ($CH_2$), 39.1 ($CH_2$), 42.2 ($CH_2$), 46.2 (CH), 58.4 (CH), 105.1 ($CH_2$), 152.7 (Cq), 214.4 (Cq); MS (EI, *m/z*) 162 ($M^+$, 69), 134 (31), 119 (29), 105 (32), 93 (79), 92 (100), 91 (80), 79 (43), 77 (39); HRMS *m/z* calcd for $C_{11}H_{14}O$ 162.1045, found 162.1048.

### 4.2. General procedure for the reduction of 4-substituted-admantan-2-ol (*Z*-16, *Z*-17 and *Z*-, *E*-18)

(a) Sodium borohydride reduction. The procedure for *Z*-**16** is given as an example. To a solution of **11** (25.8 mg, 0.01 mmol) in methanol (4 mL) was added sodium borohydride (6.7 mg, 0.02 mmol) in one portion at room temperature. After stirred for 1 h, the solution was washed with saturated ammonium chloride and extracted several times (3 mL×4) with methylene chloride. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give *Z*-**16** in 98% yield. For other reduction the yields are as follows: *Z*-**17**, 98%; *Z*- and *E*-**18** (1:1), 98%. (b) Lithium aluminum hydride reduction. The procedure for *Z*-**16** is given as an example. To a well-stirred solution of lithium aluminum hydride in dried tetrahydrofuran (THF) at 0 °C under nitrogen was added **11** (in THF) via syringe and stirred for 1 h. The solution was worked up with THF/water (1/1) and washed with water. The water layer was extracted several times (3 mL×4) with methylene chloride. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified on a silica gel column by elution with *n*-hexane/ethyl acetate and the yields are as follows: *Z*-**16**, 70%; *Z*-**17**, 71%; *Z*- and *E*-**18** (1:1), 73%.

**4.2.1. Data for 4-ethyleneketaladamantan-2$_a$-ol (*Z*-16).**[24] Colorless liquid; $\delta_H$ 1.60–2.00 (m, 12H), 2.15–2.22 (m, 1H), 3.86 (bs, 1H), 3.93–4.01 (m, 4H); $\delta_C$ 25.5 (CH), 29.0 ($CH_2$), 34.0 ($CH_2$), 34.3 (CH), 34.6 ($CH_2$), 36.07 (CH), 36.09 ($CH_2$), 41.1 (CH), 63.7 ($CH_2$), 64.4 ($CH_2$), 76.2 (CH), 111.8 (Cq); MS (EI, *m/z*) 210 ($M^+$, 32), 208 (100), 192 (36), 182 (31), 148 (32), 137 (36), 112 (31), 99 (61), 79 (45), 55 (35); HRMS *m/z* calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1258.

**4.2.2. Data for 4-ethylenethioketaladamantan-2$_a$-ol (*Z*-17).** Colorless solid; mp 87–88 °C; $\delta_H$ 1.68–1.79 (m, 6H), 1.93 (bs, 1H), 2.08–2.18 (m, 2H), 2.22–2.32 (m, 3H), 3.18–3.31 (m, 4H), 3.85 (d, $J$=7.3 Hz, OH), 3.97 (m, 1H); $\delta_C$ 25.4 (CH), 31.4 ($CH_2$), 33.7 (CH), 36.6 ($CH_2$), 36.9 ($CH_2$), 37.3 (2×$CH_2$), 38.2 ($CH_2$), 41.3 (CH), 46.2 (CH), 75.1 (Cq), 77.1 (CH); MS (EI, *m/z*) 242 ($M^+$, 92), 214 (91), 196 (63), 182 (65), 180 (45), 154 (49), 149 (76), 131 (43), 121 (100), 112 (45), 91 (61), 79 (68), 69 (52), 55 (25); HRMS *m/z* calcd for $C_{12}H_{18}OS_2$ 242.0800, found 242.0796.

**4.2.3. Data for 4-methyleneadamantan-2$_a$-ol (*Z*-18).**[25] Colorless solid; mp 86–87 °C; $\delta_H$ 1.67–2.01 (m, 11H), 2.43–2.48 (m, 2H), 3.88 (bs, 1H), 4.67, 4.77 (AX, $J=2.1$ Hz, 2H); $\delta_C$ 26.8 (CH), 33.8 ($CH_2$), 34.5 (CH), 35.9 ($CH_2$), 37.9 ($CH_2$), 38.2 (CH), 38.7 ($CH_2$), 46.1 (CH), 75.2 (CH), 106.7 ($CH_2$), 153.4 (Cq); MS (EI, *m/z*) 164 ($M^+$, 100), 94 (31), 93 (33); HRMS *m/z* calcd for $C_{11}H_{16}O$ 164.1202, found 164.1197.

**4.2.4. Data for 4-methyleneadamantan-2$_e$-ol (*E*-18).**[25] Compound *E*-**18** was not separated from its geometric isomers but its spectrum can be differentiated from the 1:1 mixture, because *Z*-**18** was obtained through an independent synthesis from *Z*-**19**. Colorless solid; $\delta_H$ 1.51–1.96 (m, 11H), 2.12–2.25 (m, 2H), 3.84 (bs, 1H), 4.60 (s, 2H); $\delta_C$ 27.4 (CH), 30.6 ($CH_2$), 32.6 ($CH_2$), 34.3 (CH), 36.6 ($CH_2$), 37.6 (CH), 39.1 ($CH_2$), 45.5 (CH), 74.7 (CH), 103.3 ($CH_2$), 155.5 (Cq); GC-MS (EI, *m/z*) 164 ($M^+$, 100), 94 (61), 93 (68).

### 4.3. General procedures for $^1$H NMR titration studies of 15 with β-CD

Solutions containing different proportions of guest-to-β-CD were prepared by stirring 5 mM of **15** with 0, 1, 2, 3, 4, 5, 7, 9, and 15 mM of β-CD solutions (15 mM stock solution in $D_2O$) in 1 mL $D_2O$ for *ca*. 3 h before measurements. The NMR spectra of all the β-CD complexes, β-CD and **15** in $D_2O$ and $CDCl_3$ with a coaxial external standard ($CDCl_3$) were recorded with a 300 MHz NMR and the results are shown in Figures 2 and 3.

**4.3.1. Synthesis of 4$_a$-hydroxyadamantan-2-one (19).** The procedure for the synthesis of **19**[25,26] is similar to that of **15**. And the amounts of reagents used are as follows: *Z*-**16** (250 mg, 1.20 mmol), PTSA·$H_2O$ (50 mg, 0.26 mmol) and 70% acetone (aq) (17 mL). The yield for **19** is 61%. Colorless solid; mp not determined (lit.[9] mp 316–320 °C); $\delta_H$ 1.82–2.06 (m, 9H), 2.39–2.51 (m, 2H), 2.72 (bs, 1H), 2.73 (bs, 1H), 4.23 (bs, 1H); $\delta_C$ 26.2 (CH), 33.2 ($CH_2$), 33.5 (CH), 35.1 ($CH_2$), 37.6 ($CH_2$), 38.9 ($CH_2$), 46.5 (CH), 54.3 (CH), 78.1 (CH), 217.7 (Cq); MS (EI, *m/z*) 166 ($M^+$, 72), 148 (53), 138 (80), 96 (55), 79 (100), 78 (76); HRMS *m/z* calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0986.

### 4.4. General procedure for the 1,3-dipolar reaction of 13–15

To a well-stirred solution of **13** (38.6 mg, 0.19 mmol) and benzohydroximinoyl chloride (43.5 mg, 0.28 mmol) in dried tetrahydrofuran (5 mL) under nitrogen was added triethylamine (31.9 mg, 0.32 mmol) via syringe and refluxed for 24 h. After cooled down to room temperature, the solution was washed with water and the water layer was extracted several times (3 mL×4) with methylene chloride. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified on a silica gel column by elution with *n*-hexane/ethyl acetate to give *E*-**20**. The yields are as follows: *E*-**20** (from **13**), 49%; *E*- and *Z*-**22** (1:1) (from **15**), 51%. Only recovered starting material **14** was obtained under this reaction condition.

**4.4.1. Data for (*E*)-4-ethyleneketalspiro[adamantane-2,5′-3′-phenyl-Δ$^2$-isoxazoline] (*E*-20).** Colorless liquid; $\delta_H$ 1.49–1.55 (m, 1H), 1.63–2.05 (m, 9H), 2.29–2.35 (m, 2H), 3.08, 3.56 (AX, $J=17.7$ Hz, 2H), 3.93–3.96 (m, 4H), 7.37–7.40 (m, 3H), 7.68–7.71 (m, 2H); $\delta_C$ 25.2 (CH), 30.8 ($CH_2$), 31.0 ($CH_2$), 32.7 ($CH_2$), 34.5 ($CH_2$), 35.7 (CH), 35.7 (CH), 44.0 ($CH_2$), 44.4 (CH), 63.8 ($CH_2$), 64.4 ($CH_2$), 90.8 (Cq), 111.5 (Cq), 126.4 (CH), 128.5 (CH), 129.7 (CH), 130.3 (Cq), 157.6 (Cq); MS (EI, *m/z*) 325 ($M^+$, 100), 179 (50), 99 (35), 91 (32), 77 (70), 55 (32); HRMS *m/z* calcd for $C_{20}H_{23}O_3N$ 325.1678, found 325.1680.

**4.4.2. Data for (*E*)-spiro[adamantan-2-one-4:5′-3′-phenyl-Δ$^2$-isoxazoline] (*E*-22).** Colorless solid; mp 131–132 °C; $\delta_H$ 1.82–1.92 (m, 3H), 2.03–2.12 (m, 5H), 2.41–2.45 (m, 1H), 2.60–2.68 (m, 3H), 2.97, 3.06 (AB, $J=16.7$ Hz, 2H), 7.36–7.40 (m, 3H), 7.60–7.63 (m, 2H); $\delta_C$ 25.8 (CH), 32.3 ($CH_2$), 33.4 ($CH_2$), 35.1 ($CH_2$), 36.6 (CH), 38.7 ($CH_2$), 43.6 ($CH_2$), 45.6 (CH), 56.2 (CH), 90.4 (Cq), 126.4 (CH), 128.6 (CH), 129.4 (Cq), 130.1 (CH), 156.6 (Cq), 214.2 (Cq); MS (EI, *m/z*) 281 ($M^+$, 100), 144 (31), 117 (47), 77 (36); HRMS *m/z* calcd for $C_{18}H_{19}O_2N$ 281.1416, found 281.1414. Anal. calcd for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98, found: C, 76.64; H, 6.83; N, 5.01.

**4.4.3. Data for (*Z*)-spiro[adamantan-2-one-4:5′-3′-phenyl-Δ$^2$-isoxazoline] (*Z*-22).** Colorless solid; mp 118–119 °C; $\delta_H$ 1.92–2.13 (m, 9H), 2.52–2.67 (m, 3H), 3.24, 3.34 (AB, $J=16.8$ Hz, 2H), 7.41 (m, 3H), 7.66 (m, 2H); $\delta_C$ 26.3 (CH), 33.2 ($CH_2$), 34.6 ($CH_2$), 36.4 (CH), 37.7 ($CH_2$), 39.1 ($CH_2$), 43.0 ($CH_2$), 45.3 (CH), 55.4 (CH), 93.7 (Cq), 126.5 (CH), 128.7 (CH), 129.7 (Cq), 130.1 (CH), 155.7 (Cq), 213.6 (Cq); MS (EI, *m/z*) 281 ($M^+$, 100), 146 (30), 144 (45), 117 (65), 91 (39), 77 (51); HRMS *m/z* calcd for $C_{18}H_{19}O_2N$ 281.1416, found 281.1422. Anal. calcd for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98, found: C, 76.55; H, 6.87; N, 5.07.

### 4.5. General procedure for the synthesis of 4-substituted-11-dichlorocyclopropylspiro-adamantane (*E*-23 and *E*-, *Z*-25)

The procedure for *E*-**23** is given as an example. To a well-stirred solution of **13** (69.5 mg, 0.34 mmol) and triethylbenzylammonium chloride (10 mg, 0.04 mmol) in chloroform (1 mL) was added 50% NaOH (aq) (1 mL) at room temperature and stirred overnight. The solution was washed with water and extracted several times (5 mL×4) with methylene chloride. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified on a silica gel column by elution with *n*-hexane/ethyl acetate to give *E*-**23**. The yields are as follows: *E*-**23**, 98%; *E*- and *Z*-**25** (1:>99), 48%.

**4.5.1. Data for (*E*)-4-ethylketal-11-dichlorocyclopropylspiroadamantane (*E*-23).** Colorless liquid; $\delta_H$ 1.21, 1.41 (AX, $J=7.4$ Hz, 2H), 1.58–2.01 (m, 12H), 3.84–3.94 (m, 4H); $\delta_C$ 25.7 (CH), 32.4 ($CH_2$), 32.9 ($CH_2$), 33.2 ($CH_2$), 33.8 ($CH_2$), 34.2 (CH), 35.2 ($CH_2$), 35.5 (CH), 37.9 (Cq), 41.9 (CH), 64.1 ($CH_2$), 64.3 ($CH_2$), 66.0 (Cq), 111.3 (Cq); MS (EI, *m/z*) 292 ($M^+$+4, 2), 290 ($M^+$+2, 10), 288 ($M^+$, 13), 253 (100), 99 (45); HRMS *m/z* calcd for $C_{14}H_{18}O_2^{35}Cl_2$ 288.0685, found 288.0682. Anal. calcd for $C_{14}H_{18}O_2Cl_2$: C, 58.14; H, 6.27, found: C, 57.99; H, 6.36. For characteristic $^1$H NMR peaks of *Z*-**23** see Fig. S-35.

**4.5.2. Data for (*Z*)-11-dichlorocyclopropylspiroadamantan-2-one (*Z*-25).** Colorless solid; mp 53–54 °C; $\delta_H$ 1.27, 1.37 (AB, $J=7.2$ Hz, 2H), 1.80–2.08 (m, 9H), 2.09–2.13 (m, 1H), 2.43 (bs, 1H), 2.64 (bs, 1H); $\delta_C$ 26.5 (CH), 30.7 ($CH_2$), 33.8 (CH), 34.7 ($CH_2$), 35.7 ($CH_2$), 38.3 ($CH_2$), 38.8 ($CH_2$), 41.2 (Cq), 45.6 (CH), 51.5 (CH), 65.9 (Cq), 214.4 (Cq); MS (EI, *m/z*) 248 ($M^+ +4$, 7), 246 ($M^+ +2$, 39), 244 ($M^+$, 61), 209 (38), 181 (87), 178 (86), 152 (33), 145 (75), 139 (56), 138 (49), 105 (39), 91 (65), 79 (100); HRMS *m/z* calcd for $C_{12}H_{14}O^{35}Cl_2$ 244.0423, found 244.0415. Anal. calcd for $C_{12}H_{14}OCl_2$: C, 58.79; H, 5.76, found: C, 58.65; H, 5.82.

**4.5.3. Data for (*E*)-11-dichlorocyclopropylspiroadamantan-2-one (*E*-25).** Which was obtained from the acid catalyzed hydrolysis of *E*-**22**, a colorless liquid; $\delta_H$ 1.15, 1.31 (AB, $J=7.3$ Hz, 2H), 1.85 (bs, 1H), 1.95–2.15 (m, 8H), 2.29–2.35 (m, 2H), 2.56 (bs, 1H); $\delta_C$ 26.3 (CH), 31.2 ($CH_2$), 34.0 (CH), 34.4 ($CH_2$), 35.5 ($CH_2$), 37.6 ($CH_2$), 38.2 ($CH_2$), 40.5 (Cq), 45.3 (CH), 52.4 (CH), 64.4 (Cq), 214.6 (Cq); MS (EI, *m/z*) 248 ($M^+ +4$, 9), 246 ($M^+ +2$, 51), 244 ($M^+$, 76), 209 (34), 181 (100), 145 (69), 91 (91), 79 (94); HRMS *m/z* calcd for $C_{12}H_{14}O^{35}Cl_2$ 244.0423, found 244.0418.

### 4.6. General procedure for the synthesis of 4-substituted-2-oxacyclopropyladamantane (*Z*-, *E*-26 and *Z*-, *E*-28)

The procedure for *Z*-, *E*-**26** is given as an example. To a well-stirred solution of **13** (40.5 mg, 0.20 mmol) in methylene chloride (2 mL) was added 70–75% *m*CPBA (48.2 mg, 0.28 mmol) at room temperature and kept stirred for 1.5 h. The solution was washed with water and the water layer was extracted several times (3 mL×4) with methylene chloride. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give *Z*-, *E*-**26**. The yields are as follows: *Z*- and *E*-**26** (1:1), 80%; *Z*- and *E*-**28** (67:33), 71%.

**4.6.1. Data for (*Z*)-4-ethyleneketal-2-oxacyclopropyladamantane (*Z*-26).** Colorless liquid; $\delta_H$ 1.33 (bs, 1H), 1.41 (bs, 1H), 1.65–1.84 (m, 7H), 1.95–2.00 (m, 1H), 2.12–2.28 (m, 2H), 2.52, 2.57 (AB, $J=4.8$ Hz, 2H), 3.88–4.02 (m, 4H); $\delta_C$ 25.9 (CH), 31.6 ($CH_2$), 34.1 ($CH_2$), 34.6 ($CH_2$), 35.0 (CH), 35.4 (CH), 36.6 ($CH_2$), 43.9 (CH), 51.5 ($CH_2$), 64.0 ($CH_2$+Cq), 64.6 ($CH_2$), 110.9 (Cq); MS (EI, *m/z*) 222 ($M^+$, 62), 221 ($M^+ -1$, 87), 192 (53), 179 (36), 151 (39), 149 (62), 99 (100), 91 (74), 79 (66), 55 (62); HRMS *m/z* calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1266.

**4.6.2. Data for (*E*)-4-ethyleneketal-2-oxacyclopropyladamantane (*E*-26).** Colorless liquid; $\delta_H$ 1.36 (bs, 2H), 1.62–1.84 (m, 5H), 1.96–2.02 (m, 5H), 2.66, 2.71 (AB, $J=4.7$ Hz, 2H), 3.86–3.94 (m 4H); $\delta_C$ 25.6 (CH), 31.9 ($CH_2$), 32.4 ($CH_2$), 34.1 ($CH_2$), 34.4 ($CH_2$), 34.6 (CH), 35.7 (CH), 44.1 (CH), 55.7 ($CH_2$), 63.2 (Cq), 64.2 (2×$CH_2$), 111.5 (Cq); MS (EI, *m/z*) 222 ($M^+$, 100), 221 (67), 193 (46), 192 (43), 149 (35), 99 (71), 91 (32); HRMS *m/z* calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1261.

**4.6.3. Data for (*Z*)-4-oxacyclopropyladamantan-2-one (*Z*-28).** Colorless solid; mp 96–98 °C; $\delta_H$ 1.86–1.91 (m, 2H), 2.01–2.11 (m, 7H), 2.18–2.21 (m, 1H), 2.37–2.41 (m, 1H), 2.60 (bs, 1H), 2.64, 2.72 (AB, $J=4.5$ Hz, 2H); $\delta_C$ 26.3 (CH), 33.0 ($CH_2$), 33.8 ($CH_2$), 34.6 (CH), 37.4 ($CH_2$), 38.7 ($CH_2$), 45.3 (CH), 54.4 ($CH_2$), 54.9 (CH), 63.9 (Cq), 214.0 (Cq); MS (EI, *m/z*) 178 ($M^+$, 60), 150 (100), 105 (31), 92 (60), 91 (34); HRMS *m/z* calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0988.

**4.6.4. Data for (*E*)-4-oxacyclopropyladamantan-2-one (*E*-28).** Colorless solid; mp 99–100 °C; $\delta_H$ 1.56 (bs, 1H), 2.00–2.19 (m, 10H), 2.59 (bs, 1H), 2.63, 2.74 (AB, $J=4.5$ Hz, 2H); $\delta_C$ 26.4 (CH), 34.3 ($CH_2$), 34.9 (CH), 35.7 ($CH_2$), 38.7 ($CH_2$), 39.0 ($CH_2$), 45.6 (CH), 52.8 ($CH_2$), 54.6 (CH), 66.4 (Cq), 214.2 (Cq); MS (EI, *m/z*) 178 ($M^+$, 68), 150 (100), 93 (32), 92 (65), 91 (30); HRMS *m/z* calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0991. Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92, found: C, 73.79; H, 8.00.

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## Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.07.075

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