BF3-Et2O Mediated Skeletal Rearrangements of Norbornyl Appended Cyclopentanediols

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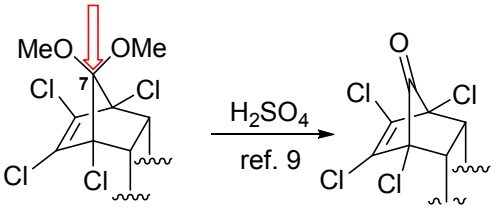
BF_3-Et_2O Mediated Skeletal Rearrangements of Norbornyl Appended Cyclopentanediols†

Chintada Nageswara Rao[b] *and Faiz Ahmed Khan*[*a]

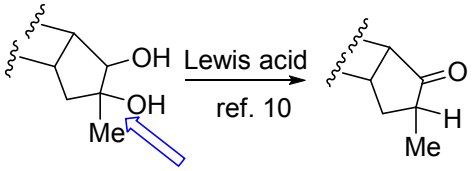
Abstract: An unusual cascade rearrangement has been noticed as a competitive reaction during the treatment of norbornyl appended cyclopentanediols to Lewis acid (LA), BF_3-Et_2O mediated pinacol-pinacolone rearrangement. Deketalization and pinacolone rearrangement occurring at two different sites in the molecule, are responsible for the observed cascade rearrangement product. However, deketalization appears to be triggering the cascade steps. The kinetically more stable pinacolone product with *exo*-Me group was observed in case of the bromo analogue. Whereas, thermodynamically more stable pinacolone product with *endo*-Me group was observed in case of chloro analogue. Epimerization via tautomerization of one diastereomer to the other diastereomer under Lewis acid reflux conditions is possible. On the contrary, the diol equivalent epoxides provide only the diastereomeric mixture of pinacolone products under similar LA reaction conditions. The lower yields observed in case of the epoxides are due to unwanted side reactions taking place between the two competitive reactive centers, namely, ketal and epoxide. Further, a sequence of elimination, nucleophilic substitution and Ritter type hydrolysis reactions of the epoxides resulted unexpected elimination products. This transformation not only facilitates a regioselective epoxide opening, but also provides a new route for the preparation of allylic amides of norbornyl appended cyclopentane ring system.

Introduction

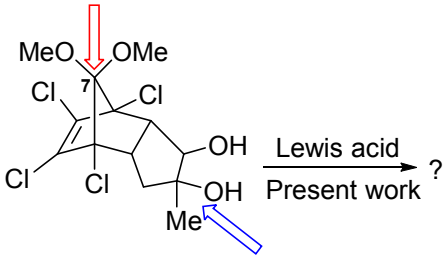
Cascade reactions involve two or more consecutive bonds formation or disruption in one pot, via an unstable intermediate.[1,2] The reactive species generated in these processes are rather difficult to isolate. Once the cascade process is initiated, the reaction path could no longer be controlled. Since, the initiated process should terminate at one point of time with or without reaching to the final product; lower yields are often noticed in these transformation reactions. Nevertheless, there is a great advantage of these chemical reactions due to their synthetic applications and the complexity of the products formed in a single transformation.[3,4] In general, polycyclic ketones undergo a skeletal rearrangement via carbocation intermediate in acidic conditions.[5,6] One of the earliest acid-catalyzed transformations discovered by Rudolph Fittig in 1860 involving carbocation intermediate is pinacol to pinacolone rearrangement. This classical rearrangement was utilized for synthesizing a variety of strained and highly substituted aldehydes and ketones.[7] Although, many methods were developed over the years for this transformation by using variety of acids,[8] to the best of our knowledge there is no precedent literature in which deketalization is used as the driving force for the cascade steps, especially, in a tricyclic system. With regard to these skeletal rearrangements, suitably substituted norbornyl derivatives could be appropriate substrates for the skeletal rearrangements via carbocation intermediate.



eq. 1



eq. 2



eq. 3

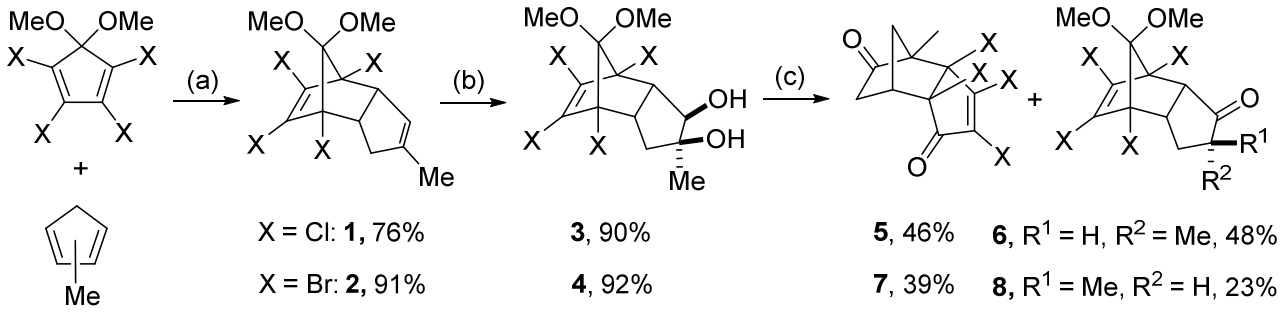
It should be noted that, a ketal embedded bicyclic system would normally provide a deketalization product upon treatment with acid (eq. 1).[9] Whereas, vicinal diol with methyl substitution at one of the alcoholic carbon center on a cyclopentane ring would exclusively undergo a pinacol-pinacolone type rearrangement, under afore-mentioned acidic reaction conditions (eq. 2).[10] However, we were curious to check the outcome when a bicyclic system possessing both ketal group (at C-7 position) as well as a cyclopentane ring with methyl substitution at one of the vicinal diol (eq.3), is subjected to a Lewis acid. Whether the two remote functionalities, namely, ketal and diol would act in synergy?

Results and Discussion

In order to explore the reactivity of norbornyl appended cyclopentanediols, the substrates **3** or **4** (Scheme 1) were chosen for the Lewis acid (BF_3-Et_2O) mediated pinacol-pinacolone rearrangement. The vicinal diols **3**, **4** were synthesized from the corresponding Diels-Alder adducts **1**, **2** by selective hydroxylation of *exo*-face in presence of catalytic OsO_4 and co-oxidant

NMO (Scheme 1). The chloro adduct **1** was prepared by following the procedure developed in our laboratory.[11] A similar protocol can be followed for the preparation of the bromo derivative **2**, from the corresponding tetrabromo-5,5-dimethoxycyclopentadiene and methylcyclopentadiene under toluene reflux, over a period of 4 h in presence of catalytic amount of hydroquinone and epichlorohydrin. The methyl substitution was intentionally chosen to provide a tertiary alcohol to eventually facilitate carbocation mediated transformations.

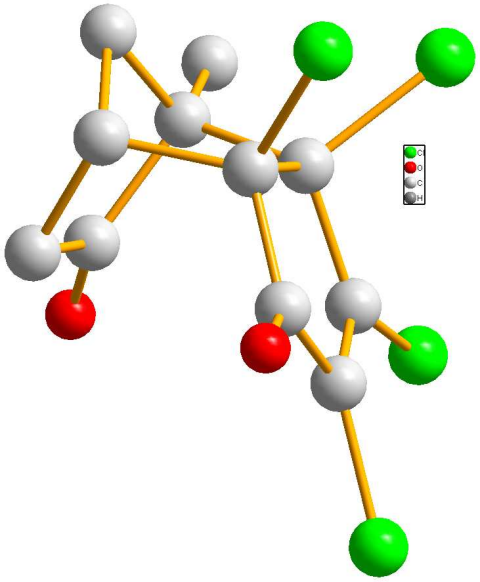
Scheme 1: Skeletal rearrangement of the norbornyl appended cyclopentanediols 3, 4



(a)hydroquinone (5 mol%), epichlorohydrin (5 mol%), toluene, reflux, 4 h; (b) OsO_4 (2 mol%), NMO, acetone:H_2O (3:1), rt, 9 h; (c) BF_3-Et_2O, toluene, reflux, 5 h.

When the *cis*-diol **3** was subjected to BF_3-Et_2O in toluene reflux, a separable mixture of two products was obtained. Unexpectedly, one of them turned out to be a cascade-rearranged product (**5**) and the other was a pinacol-pinacolone rearranged product (**6**), with an excellent overall yield. Similar products **7** and **8** were observed in case of bromo derivative (Scheme 1). The cascade rearrangement product **5** was unambiguously confirmed by single crystal X-ray analysis (Figure1).[12]

Figure1: X-ray crystal structure of the cascade-rearranged product 5



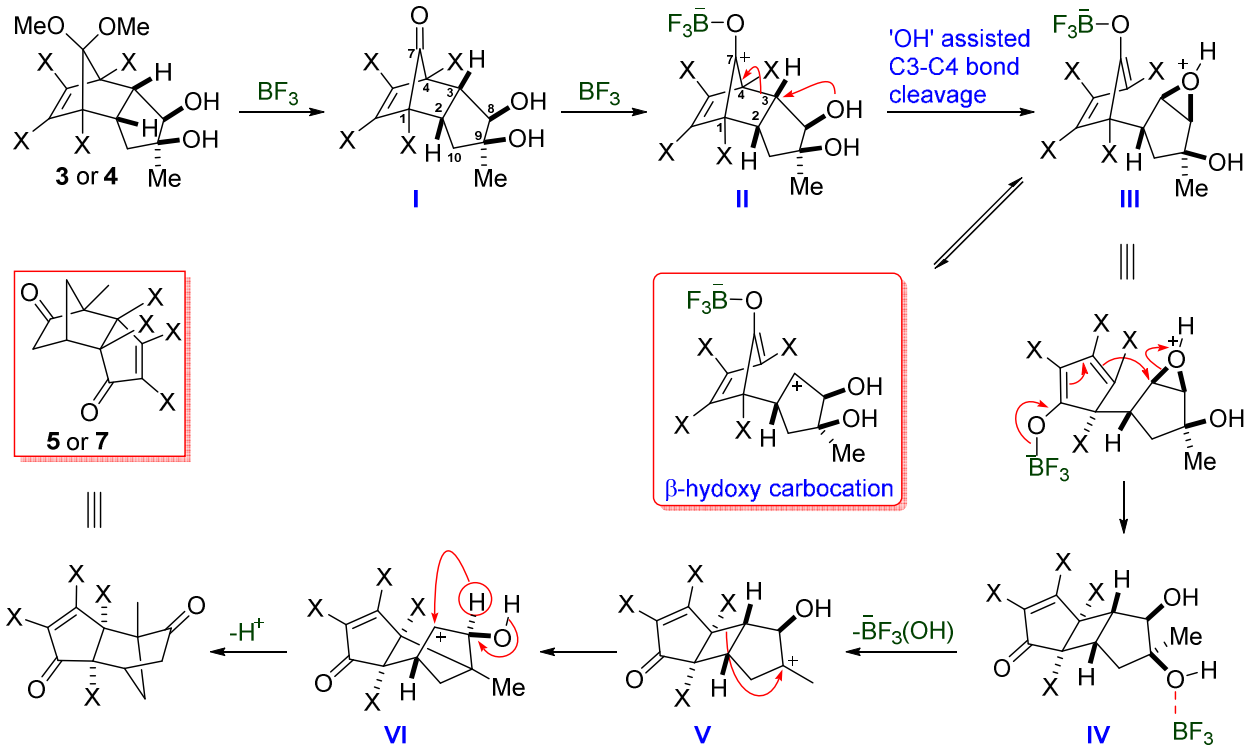
In case of chloro derivative the pinacolone product **6** was isolated as a single isomer with methyl group having *endo* position. Whereas, in case of bromo derivative **8**, the ^{1}H NMR indicate the position of methyl group having *exo* orientation as a major component (Scheme 1) along with traces of other isomer. Nevertheless, the structure confirmation of **8** was fulfilled by 2D NMR (COSY, HMQC and HMBC) analysis.

A possible explanation for the formation of products **5** or **7** and **6** or **8** is as follows; since the substrate **3** or **4** having two reactive centers, when the Lewis acid (LA) approaches the diol reactive center first, the reaction proceeds via pinacol-pinacolone rearrangement to give either **6** or **8**. Whereas, if the LA approaches the ketal reaction center first, it will undergo a series of C-C bond breaking and making processes to give-rise to a cascade-rearranged product as shown in Scheme 2.

Under Lewis acid reaction condition, ketal hydrolysis followed by the coordination of LA to the formed carbonyl intermediate (**I**) would lead to the generation of carbocation at C7 center of **II**. At this stage, either C1-C2 or C3-C4 bond cleavage may initiate further cascade steps. However,

hydroxyl group assisted cleavage of C3-C4 bond followed by generation of stable oxonium ion (**III**) would by-pass the C1-C2 bond cleavage path way. Alternatively, the generation of a β-hydroxy carbocation (scheme 2) via C3-C4 bond cleavage with subsequent formation of an oxonium ion could also be expected.

Scheme 2: A plausible mechanism for the formation of cascade products (5 or 7)

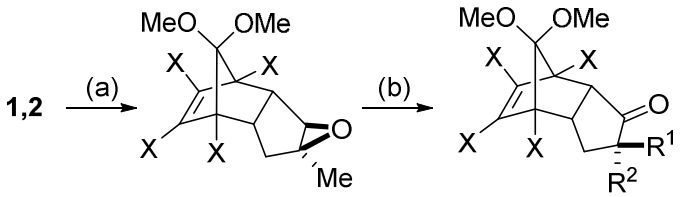


It is also possible that, these two competing reactive intermediates (oxonium ion and β-hydroxy carbocation) are in equilibrium with each other. However, skeletal re-organization of intermediate **III** followed by double bond migration via 1,3-sigmatropic shift would regenerate the carbonyl of the tricyclic intermediate (**IV**) with expulsion of LA. The vicinal diol of tricyclic intermediate can again react with LA to generate the β-hydroxy carbocation (**V**) and subsequent migration of the back bond of the central four-membered ring could facilitate the second β-hydroxy carbocation (**VI**). Hydride shift followed by the removal of proton would thus provide the cascade product **5** or **7**. A rational explanation for the high stereo selection of the cascade

process would stem from the neighboring group effect or anchimeric assistance on the hydroxy group assisted C-C bond cleavage or the generation of β-hydroxy carbocation via C-C bond cleavage (scheme 2).

As can be seen, for the formation of product **5** or **7** both ketal and diol functionalities in **3** or **4** are essential for the Lewis acid mediated cascade rearrangement. If deketalization and the subsequent formation carbocation at C7 center is the driving force for the cascade steps, the diol equivalent epoxides **9** or **10** (table 1) would provide only the pinacolone products **6** or **8**, as the epoxide functional group is less tolerant than the corresponding vicinal diol, towards LA. With this intention, the methyl substituted epoxides **9** and **10** were prepared from the corresponding Diels-Alder adducts **1** and **2** by *m*-CPBA mediated epoxidation with excellent yields. When the chloro epoxide **9** was refluxed with BF_3-Et_2O in toluene, a separable mixture of two products **6** and **11** was observed in 47 % overall yield. A similar mixture of products **8** and **12** was also observed in case of the bromo epoxide **10**. However, at room temperature, a single diastereomer **11** in case of the chloro derivative, **8** in case of bromo derivative was obtained (table 1). The poor reaction yield in case of epoxides is probably due to the unwanted side reactions occurring after pinacol rearrangement. Once pinacol-pinacolone rearrangement occurred, the next possible reactive center is ketal for the LA. In order to operate the cascade steps, a stable carbocation or neighboring group assistance is essential after deketalization, which is unlikely in case of epoxides. Hence, further deketalization of pinacolone product may lead to the decomposition of the product, thus lower yields were noticed.

Table 1: Pinacol-type rearrangement of norbornyl appended cyclopentane epoxides 9, 10



X = Cl: **9**, 87%

X = Br: **10**, 92%

6, R^1 = H, R^2 = Me
11, R^1 = Me, R^2 = H

8, R^1 = Me, R^2 = H
12, R^1 = H, R^2 = Me

temperature	X	time (h)	% yield	
reflux	Cl	5	18 (**6**)	29 (**11**)
	Br	5	38 (**8**)	17 (**12**)
rt	Cl	8	--	44 (**11**)
	Br	8	37 (**8**)	--

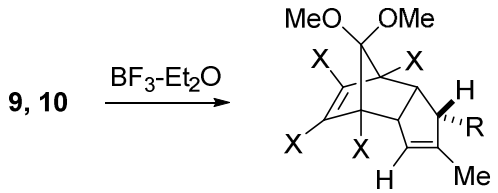
(a) m-CPBA, buffer (PH=7), DCM, 0 to 30 ^oC, 10-14 h; (b) BF_3-Et_2O, toluene.

The possible explanation for the formation of a mixture of two diastereomers **6**, **11** or **8**, **12** at higher temperature is due to the epimerization of one diastereomer to other thermodynamically more stable product in Lewis acid reflux conditions. In order to rationalize the phenomenon, the pinacol product **11** was treated with BF_3-Et_2O in toluene and heated over a period of 24 h at 120 ^oC. Interestingly, two diastereomers **6**, **11** (1:1) were formed in the reaction mixture. This observation clearly suggests that an epimerization via tautomerization of **11** to the corresponding diastereomer **6** under LA condition is occurring.

Since the reactivity of these epoxides towards LA appeared to be vulnerable, we extended the study of epoxides to a nucleophilic ring opening reaction. We predicted that, the use of nucleophilic solvents instead of non-polar solvent toluene would have an added advantage because it can serve two purposes at the same time; as a reaction medium and as a source of

nucleophile. With this prediction, the reaction was carried out in acetonitrile under LA reflux conditions. To our surprise, a completely different set of products was obtained when the epoxides **9** or **10** were subjected to BF_3-Et_2O. Depending on the conditions employed, elimination products **13-16** were obtained in moderate to good yields as mentioned in Table 2. When the chloro analogue of epoxide **9** was subjected to BF_3-Et_2O reflux conditions in benzonitrile, elimination product **15** was furnished in 49% yield (Table 2). Although, the epoxide opening in the presence of alkylnitriles is a common nucleophilic ring opening transformation in the literature.[13,14] Nevertheless, epoxide opening followed by elimination under Lewis acid conditions is quite uncommon. When the temperature was reduced from reflux to room temperature, the elimination product **13** (61%) was formed as a major component along with **16** (10%). Further reduction of reaction temperature from ambient to 0 ^oC, the elimination product **16** was observed along with traces of product **13**.

Table 2: Nucleophilic ring opening followed by the elimination of norbornyl appended cyclopentane epoxides 9, 10



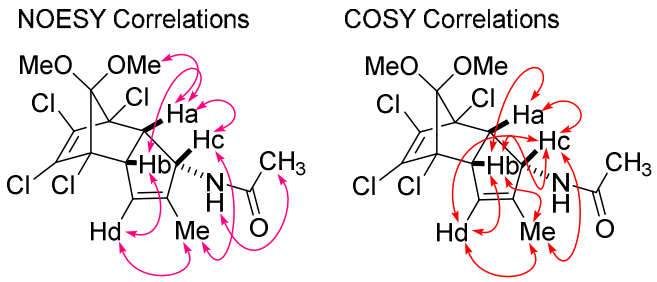
13-16

temperature	solvent	X	time (h)	R	% yield (product)
reflux	CH_3CN	Cl	3	$NHCOCH_3$	71 (**13**)
	CH_3CN	Br	3	$NHCOCH_3$	57 (**14**)
	PhCN	Cl	3	NHCOPh	49 (**15**)
rt	CH_3CN	Cl	4	$NHCOCH_3$ OH	61 (**13**) 10 (**16**)

0 ^{o}C	CH_3CN	Cl	0.75	OH	64 (**16**)

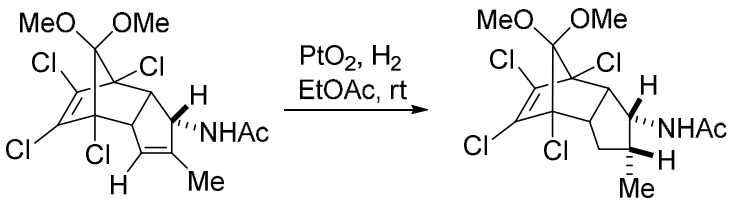
The formation of allylic alcohol **16** indicates that the water is acting as a nucleophile during aqueous workup. In our attempt to use water as a nucleophile, we treated the epoxide **9** to tetrabutylammonium bisulphate (Bu_4NHSO_4) in THF-H_2O (1:1) under reflux conditions, a reported procedure,[15] the elimination product **16** was observed in 40% yield. Under above reaction conditions, elimination of epoxide and the subsequent nucleophilic attack of water (H_2O) have been occurring in a single transformation.

Figure 2: NOESY and COSY correlations of product 13



The structure confirmation of **13** was carried out by careful analysis of 2D NMR (NOESY and COSY) as represented in Figure 2. Although, the 2D NMR data confirm the position of double bond in product **13**, nevertheless, a chemical method may simply fix the position of amide group and the double bond. For that purpose, the compound **13** was subjected to PtO_2-H_2 in ethyl acetate at room temperature.

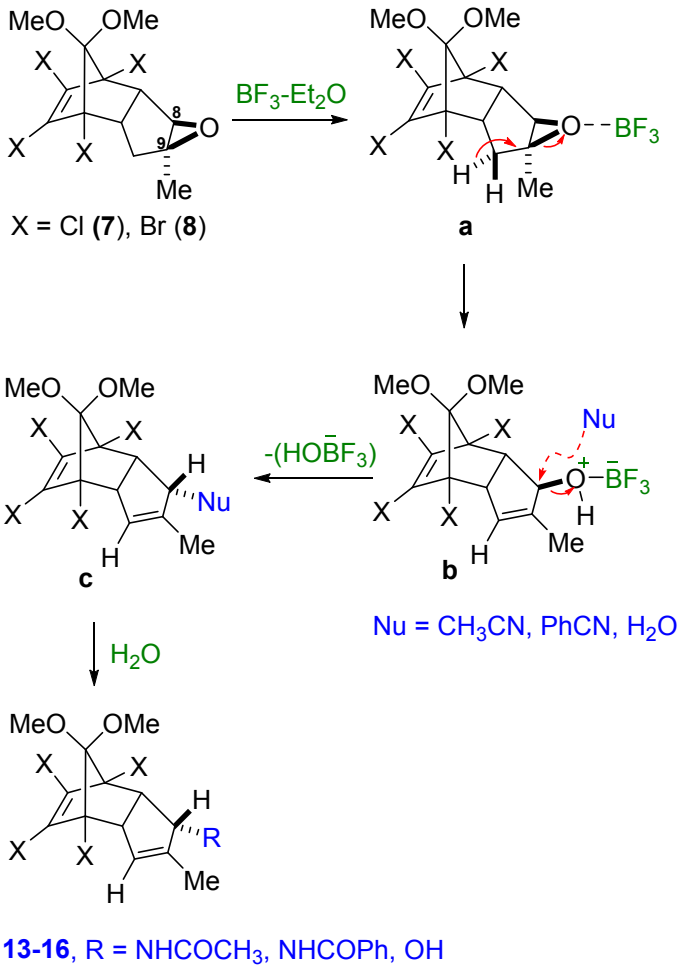
Scheme 3: Selective reduction of the allylic double bond in 13 leading to the amide 17



13 **17**, 90%

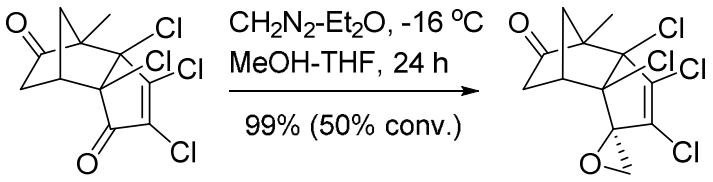
The double bond reduction was preceded smoothly to furnish the product **17** in excellent yield. ^{1}H NMR of the reduced product clearly indicates the product **17**, thus proved the position of amide group and the double bond of compound **13** as mentioned in the scheme 3.

Scheme 4: A plausible mechanism for the formation of products 13-16



Based on the experimental results, a plausible mechanism for the formation of products **13-16** would be as follows; coordination of the LA (BF_3-Et_2O) to the epoxide **9** or **10**, followed by the elimination of epoxide **a** leading to the intermediate **b**. The attack of nucleophile at C-8 carbon of **b** from *endo*-face with the expulsion of $HOBF_3$ would lead to the intermediate **c** (scheme 4). The subsequent Ritter type hydrolysis of the nitrile group in intermediate **c** would provide the respective hydrolysis products (**13-16**) as depicted in Scheme 4.

Scheme 5: Selective oxirane formation of the conjugate carbonyl group of 5



5 **18**

Having observed an interesting molecular scaffold **5** and **7** through a simple LA mediated cascade rearrangement; it would be worth considering the synthetic utility of these molecules. In this regard, we treated the cascade product **5** to ethereal solution of diazomethane in MeOH-THF solution[16,17] and the conjugated carbonyl of **5** was selectively transformed to the corresponding oxirane derivative **18** without affecting the isolated carbonyl in quantitative yield at -16 °C over a period of 24 h (Scheme 5).

Conclusions

In this study, we investigated BF_3-Et_2O mediated skeletal rearrangements of norbornyl appended cyclopentanediols wherein hydroxy group assisted C-C bond cleavage (anchimeric assistance) led to the formation of cascade-rearranged product. Depending on the approach of Lewis acid (LA), two different products were observed: If the LA reacts first with the ketal reactive center, a cascade rearranged product would be formed and if the LA approaches diol reactive center first, the pinacolone product would be formed. The diol equivalent epoxides provided a diastereomeric mixture of pinacolone products. Epimerization via tautomerization of one diastereomer to the other thermodynamically more stable diastereomer in Lewis acid medium was noticed. A sequence of elimination, nucleophilic substitution and Ritter type hydrolysis reactions of epoxides were observed in single transformation. This transformation facilitates a method for the

regio and stereoselective synthesis of allylic amides of the cyclopentane annulated norbornyl building blocks.

Experimental section

General Methods: All reactions were performed in oven dried apparatus under nitrogen atmosphere. Commercial solvents and reagents were distilled prior to use. Melting points were obtained in open capillary tubes and are uncorrected. Infrared spectra were recorded as KBr pellets (solids), or as thin films on NaCl flats (liquids). ^{1}H NMR was recorded at 400 MHz unless otherwise mentioned 500 or 600 MHz. Proton decoupled ^{13}C NMR was recorded at 100 MHz unless otherwise mentioned 125 or 150MHz. 2D NMR experiments were conducted for the structure confirmation of some of the compounds (see supporting information for COSY, HMQC&HMBC for **8** and NOESY&COSY of **13**). Single crystal X-ray analysis was carried out for the structure elucidation of compounds **5** (see supporting information for CIF data files). HRMS were recorded using electron spray ionization/electron ionization (ESI/EI) or desorption chemical ionization/chemical ionization (DCI/CI) methods using TOF, MS analyzers respectively.

(3aR,4S,7S,7aS)-4,5,6,7-tetrabromo-8,8-dimethoxy-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-methanoindene (2): To a stirred solution of 4.8 g of freshly cracked methyl cyclopentadiene was added a mixture of 5 g of 1,2,3,4-tetrabromo-5,5-dimethoxy-cyclopenta-1,3-diene and a catalytic hydroquinone in 40 mL of toluene at room temperature over a period of 10 minutes. The mixture was refluxed for 4 h. After completion of the starting material, the toluene and excess methyl cyclopentadiene were distilled off under reduced pressure and the residue was subjected to silica gel column chromatography to furnish the adduct **2** in excellent yield. R_f (5% Ethyl acetate in hexane) 0.6, colorless crystalline solid, mp 78 ^{o}C, yield 91% (5.37 g, 10.29

mmol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (dd, 1H, *J* = 1.7, 3.4 Hz), 3.70-3.67 (m, 1H), 3.65 (s, 3H), 3.58 (s, 3H), 3.33-3.28 (m, 1H), 2.32-3.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 126.0, 122.4, 120.2, 113.6, 72.0, 62.8, 52.9, 51.6, 51.0, 36.2, 16.7; IR (KBr) 2900, 1640, 1600, 1370, 1250 cm^{-1}; HRMS (DCI) Calc. for $C_{13}H_{14}O_2Br_4$ $[M]^+$, 517.772; Found, 517.772.

(1R,2S,3aS,4S,7S,7aS)-4,5,6,7-tetrachloro-8,8-dimethoxy-2-methyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoindene-1,2-diol (3): To a stirred solution of adduct **1** (560 mg, 1.63 mmol) in acetone (6.6 mL), was added OsO_4 (7.3 mg, 0.03 mmol), NMO (240 mg, 1.78 mmol) followed by distilled water (2.2 mL). The reaction mixture was stirred at room temperature for 8.5 h, and then the reaction mixture was filtered through silica pad and washed with ethyl acetate. The solvent was removed under reduced pressure. The crude reaction mass was purified by silica gel column chromatography to furnish pure crystalline material **3** in excellent yield. R_f (40% Ethyl acetate in hexane) 0.4, colorless crystalline solid, mp 128-130 ^{o}C, yield (566 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (s, 3H), 3.55 (s, 3H), 3.47 (d, 1H, *J* = 7.6 Hz), 3.37-3.30 (m, 2H), 3.03 (dd, 1H, *J* = 10.0, 7.3 Hz), 2.28 (bs, 1H), 2.00 (dd, 1H, *J* = 14.0, 8.3 Hz), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.7, 129.4, 115.5, 80.9, 77.5, 77.4, 76.8, 59.1, 52.5, 51.7, 50.8, 35.9, 24.3; IR (KBr) 2900, 1600, 1440, 1370, 1250 cm^{-1}; HRMS (CI) Calc. for $C_{13}H_{16}O_4Cl_4$ $[M\text{-}Cl]^+$, 341.0114; Found, 341. 0120.

(1R,2S,3aS,4S,7S,7aS)-4,5,6,7-tetrabromo-8,8-dimethoxy-2-methyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoindene-1,2-diol (4): R_f (40% Ethyl acetate in hexane) 0.4, colorless crystalline solid, mp 132-134 ^{o}C, yield 92% (1.0 g, 1.80 mmol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 3.59 (s, 3H), 3.60-3.33 (m, 2H), 3.14 (dd, 1H, *J* = 7.9, 2.3 Hz), 2.00 (dd, 1H, *J* = 13.1, 7.9 Hz), 1.80-1.72 (m, 1H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.2, 125.4,

115.5, 80.5, 76.7, 70.8, 69.7, 60.5, 53.1, 52.6, 51.7, 35.8, 24.4; IR (KBr) 2900, 1600, 1440, 1370, 1250 cm^{-1}; Anal. Calc. for $C_{13}H_{16}O_4Br_4$: C, 28.09; H, 2.90. Found: C, 27.91; H, 2.71.

(3aR,4R,7S,7aR)-2,3,3a,7a-tetrachloro-4-methyl-3a,4,7,7a-tetrahydro-1H-4,7-methanoindene-1,5(6H)-dione (5): To a stirred solution of substrate (100 mg, 0.26 mmol) in toluene (2 mL), was added BF_3-Et_2O (0.84 mmol). The reaction mixture was stirred for 10 minutes at room temperature and then refluxed at 120 ^oC. After 5 h the reaction mixture was quenched with ice (2 g). The reaction mixture was extracted with ethyl acetate (3x5 mL), combined organic layers were washed with saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography to furnish cascade rearranged product **5** along with pinacol-pinacolone rearranged product **6**. R_f (10% Ethyl acetate in hexane) 0.5, colorless crystalline compound, mp 163-164 ^oC, yield 46% (38 mg, 0.12 mmol); ^1H NMR (400 MHz, $CDCl_3$) δ 3.11 (dd,1H, *J* = 1.7, 4.3 Hz), 2.774 (ddd, 1H, *J* = 2.0, 4.9, 11.7 Hz), 2.31 (dd, 1H, *J* = 5.1, 19.3 Hz), 1.94 (dd, 1H, *J* = 4.9,19.4 Hz), 1.85 (dd, 1H, *J* = 1.5, 11.7 Hz), 1.41 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 208.7, 188.2, 161.5, 132.7, 80.9, 80.3, 63.5, 62.1, 45.3, 44.0, 13.0; IR (KBr) 2990, 1744, 1589, 1454, 1238, 1204 cm^{-1}; HRMS (EI) Calc. for $C_{11}H_8O_2Cl_4$ $[M]^+$, 311.9278; Found, 311.9264.

(2R,3aS,4S,7S,7aS)-4,5,6,7-tetrachloro-8,8-dimethoxy-2-methyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-one (6): R_f (5% Ethyl acetate in hexane) 0.3, colorless solid compound, mp 110 ^oC, yield 48% (46 mg, 0.13 mmol); ^1H NMR (400 MHz, $CDCl_3$) δ 3.54 (s, 3H), 3.48 (s, 3H), 3.37-3.26 (m, 2H), 2.40-2.28 (m, 2H), 1.19-1.10 (m, 1H), 0.92 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.0, 130.1, 129.5, 115.2, 78.1, 74.8, 57.5, 52.7, 51.8,

46.7, 45.4, 28.3, 13.4. IR (KBr) 2962, 1739, 1641, 1454, 1031, 893 cm^{-1}; HRMS (DCI) Calc. for $C_{13}H_{14}O_3Cl_4$ $[M\text{-}Cl]^+$, 323.001; Found, 323.003.

(3aR,4R,7S,7aR)-2,3,3a,7a-tetrabromo-4-methyl-3a,4,7,7a-tetrahydro-1H-4,7-methanoindene-1,5(6H)-dione (7): R_f (10% Ethyl acetate in hexane) 0.5, colorless crystalline compound, mp 160 ^oC, yield 39% (35 mg, 0.07 mmol); ^1H NMR (400 MHz, $CDCl_3$) δ 3.22 (dd, 1H, *J* = 1.7, 3.4 Hz), 2.79 (ddd, 1H, *J* = 2.0, 4.6, 11.7 Hz), 2.26 (dd,1H, *J* = 5.2, 19.3 Hz), 1.90 (dd, 1H, *J* = 4.6, 19.3 Hz), 1.85 (d, 1H, *J* = 1.2 Hz), 1.48 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 207.7, 188.9, 159.4, 127.6, 78.8, 71.9, 64.0, 46.3, 44.7, 41.6, 15.9; IR (KBr) 2850, 1720, 1530, 1180, 1100, 820 cm^{-1}; HRMS (CI) Calc. for $C_{11}H_8O_2Br_4$ $[M\text{-}Br]^+$, 408.807; Found, 408.823.

(2S,3aS,4S,7S,7aS)-4,5,6,7-tetrabromo-8,8-dimethoxy-2-methyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-one (8): R_f (5% Ethyl acetate in hexane) 0.4, colorless solid compound, mp 140 ^oC, yield 23% (22 mg, 0.04 mmol); ^1H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 3,59 (s, 3H), 3.35 (td, 1H, *J* = 8.8 Hz), 3.16 (d, 1H, *J* = 8.8 Hz), 2.30 (dd, 1H, *J* = 10.4, 14.6 Hz), 2.02-1.95 (m, 1H), 1.64-1.55 (m, 1H), 1.04 (d, 3H, *J* = 6.8 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 215.0, 125.4, 125.3, 114.1, 71.6, 69.0, 58.9, 53.1, 51.8, 48.4, 43.8, 28.5, 15.1; IR (KBr) 2900, 2850, 1720, 1560, 1440, 1300, 1240, 960, 870 cm^{-1}; HRMS (DCI) Calc. for $C_{13}H_{14}O_3Br_4$[M-Br]$^+$, 454.849; Found, 454.855.

(1aR,1bS,2S,5S,5aS,6aS)-2,3,4,5-tetrachloro-7,7-dimethoxy-6a-methyl-1b,2,5,5a,6,6a-hexahydro-1aH-2,5-methanoindeno[1,2-b]oxirene (9): To a stirred solution of substrate **1** (1.5 g, 4.36 mmol) in dichloromethane (20 mL), was added sodium potassium phosphate buffer, pH=7 (12 mL) followed by m-CPBA (1.87 mmol) at ice bath temperature (0-5 ^oC). After 10 h, the organic layer was separated and washed with distilled water (4 mL), brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. To the crude reaction

mixture, 10% ethyl acetate in hexane was added and filtered through a neutral alumina pad to remove acid impurities and the purification was carried out on alumina column to afford the viscous liquid **9** in very high yield. R_f (10% Ethyl acetate in hexane) 0.6, viscous liquid, yield 87% (1.36g, 3.79 mmol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (s, 3H), 3.53 (s, 3H), 3.24 (s, 1H), 3.19 (d, 1H, *J* = 7.8 Hz), 3.02-2.97 (m, 1H), 2.04 (dd, 1H, *J* = 9.0, 15.4 Hz), 1.70 (dd, 1H, *J* = 3.2, 15.4 Hz), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.3, 129.8, 113.7, 77.7, 77.2, 75.5, 68.7, 63.7, 56.3, 52.3, 51.6, 31.6, 17.8; IR (KBr) 2950, 2812, 1604, 1441, 1185, 915 cm^{-1}; HRMS (DCI) Calc. for $C_{13}H_{14}O_3Cl_4$ [M-Cl]$^+$, 323.001; Found, 323.001.

(1aR,1bS,2S,5S,5aS,6aS)-2,3,4,5-tetrabromo-7,7-dimethoxy-6a-methyl-1b,2,5,5a,6,6a-hexahydro-1aH-2,5-methanoindeno[1,2-b]oxirene (10): R_f (10% Ethyl acetate in hexane) 0.6, colorless solid compound, mp 79-80 ^{o}C, yield 92% (1.0 g, 1.86 mmol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (s, 3H), 3.57 (s, 3H), 3.31 (s, 1H), 3.22 (d, 1H, *J* = 7.8 Hz), 3.08 (td, 1H, *J* = 3.4, 7.8 Hz), 2.07 (dd,1H, *J* = 9.0, 15.4 Hz), 1.78 (dd,1H, *J* = 3.4, 15.4 Hz), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.9, 125.6, 114.3, 71.2, 70.0, 69.0, 63.9, 57.8, 53.9, 52.8, 51.6, 31.7, 17.8; IR (KBr) 2955, 2810, 1600, 1441, 1190, 915 cm^{-1}; HRMS (DCI) Calc. for $C_{13}H_{14}O_3Br_4$[M-Br]$^+$, 454.8493; Found, 454.8545.

(2S,3aS,4S,7S,7aS)-4,5,6,7-tetrachloro-8,8-dimethoxy-2-methyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-one (11): To a stirred solution of compound **7** (50 mg, 0.14 mmol) in toluene (1.8 mL), was added BF_3-Et_2O (0.42 mmol) at room temperature. After 8 h, the reaction mixture was quenched with ice (2 g). The organic compound was extracted with ethyl acetate (3x5 mL), combined organic layers were washed with saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. After evaporation of solvent under reduced pressure, the crude reaction mixture was purified by silica gel column chromatography to obtain pinacolone product

9. When the same reaction was conducted under toluene reflux conditions afforded the separable mixture of two diastereomers of pinacolone products. R_f (5% Ethyl acetate in hexane) 0.4, colorless solid compound, mp 142 ^oC, yield 44% (22mg, 0.06 mmol); ^1H NMR (400 MHz, $CDCl_3$) δ 3.53 (s, 3H), 3.48 (s, 3H), 3.21 (t, 1H, J = 9.1 Hz), 3.06 (d, 1H, J = 9.1 Hz), 2.21 (dd, 1H, J = 10.5, 14.6 Hz), 1.96-1.85 (m, 1H), 1.58-1.49 (m, 1H), 0.97 (d, 3H, J = 6.8 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 215.0, 129.3, 128.9, 114.1, 77.7, 76.1, 57.6, 52.6, 51.7, 46.7, 43.3, 28.3, 15.1; IR (KBr) 1700, 1580, 1420, 1150, 890, 760 cm^{-1}; HRMS (DCI) Calc. for $C_{13}H_{14}O_3Cl_4$ $[M\text{-}Cl]^+$, 323.001; Found, 323.003.

(2R,3aS,4S,7S,7aS)-4,5,6,7-tetrabromo-8,8-dimethoxy-2-methyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-one (12): R_f (5% Ethyl acetate in hexane) 0.3, colorless solid compound, mp 117 ^oC, yield 17% (17 mg, 0.03 mmol); ^1H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 3.59 (s, 3H), 3.48-3.37 (m, 2H), 2.49-2.37 (m, 2H), 1.27-1.18 (m, 1H), 0.97 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9, 125.9, 125.7, 115.2, 71.4, 67.2, 58.8, 53.2, 51.8, 48.7, 45.1, 28.3, 13.3. IR (KBr) 2984, 1756, 1660, 1475, 1050, 914 cm^{-1}; HRMS (DCI) Calc. for $C_{13}H_{14}O_3Br_4$ $[M\text{-}Br]^+$, 454.849; Found, 454.855.

N-((1S,3aS,4S,7S,7aS)-4,5,6,7-tetrachloro-8,8-dimethoxy-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-yl)acetamide (13): To a stirred solution of compound **9** (100 mg, 0.28 mmol) in acetonitrile (3 mL) was added BF_3-Et_2O (0.83 mmol) at room temperature, the reaction mixture was refluxed for 2 h then the reaction mixture was quenched with ice (4 g). The organic compound was extracted with ethyl acetate (3x10 mL), combined organic layers were washed with saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography to furnish colorless crystalline compound **13**. R_f (40% Ethyl acetate in hexane)

0.4, mp 164 ^{o}C, yield 71% (100 mg, 0.28 mmol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (s, 1H), 5.35 (d, 1H, *J* = 8.8 Hz), 4.68 (d, 1H, *J* = 8.8 Hz), 3.68 (d, 1H, *J* = 7.8 Hz), 3.59 (s, 3H), 3.54 (s, 3H), 2.91 (dd, 1H, *J* = 2.6, 7.8 Hz), 1.99 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 169.0 145.7, 129.5, 127.3,124.3, 113.9, 78.0,76.5, 59.6, 58.3, 56.7, 52.6, 51.6, 23.2, 14.2; IR (KBr) 3321, 2942, 2847, 1654, 1528,1189 cm^{-1}; HRMS (ESI) Calc. for $C_{15}H_{17}NO_3Cl_4$ $[M+H]^+$ 400.0041; Found, 400.0041.

N-((1S,3aS,4S,7S,7aS)-4,5,6,7-tetrabromo-8,8-dimethoxy-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-yl)acetamide (14): R_f (40% Ethyl acetate in hexane) 0.4, colorless crystalline compound, mp 180 ^{o}C, yield 57% (100 mg, 0.17 mmol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (dd, 1H, *J* = 1.7,4.2 Hz), 5.39 (d, 1H, *J* = 9.1), 4.78 (dt, 1H, *J* = 1.0, 1.5, 9.1 Hz), 3.74-3.70 (1H, m), 3.62 (s, 3H), 3.58 (s, 3H), 2.98 (dd, 1H, *J* = 2.7, 7.8 Hz), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 145.3, 125.7, 124.6, 122.9, 113.9, 71.3, 69.8, 61.2, 59.7, 56.6, 53.0, 51.6, 23.4, 14.2; IR (KBr) 3267, 2941, 2847, 1644, 1557, 1447, 1185 cm^{-1}; HRMS (CI) Calc. for $C_{15}H_{17}NO_3Br_4$ $[M-Br]^+$, 495.876; Found, 495.876.

N-((1S,3aS,4S,7S,7aS)-4,5,6,7-tetrachloro-8,8-dimethoxy-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-yl)benzamide (15): R_f (30% Ethyl acetate in hexane) 0.4, colorless crystalline compound, mp 176 ^{o}C, yield 49% (40 mg, 0.09 mmol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, 2H, *J* = 7.3 Hz), 7.45 (t, 1H, *J* = 7.3 Hz), 7.37 9 (t, 2H, *J* = 7.6 Hz), 5.99 (d, 1H, *J* = 8.7 Hz), 5.40 (s, 1H), 4.83 (d, 1H, *J* = 8.7 Hz), 3.53 (s, 3H), 3.49 (s, 3H), 2.98 (dd, 1H, *J* = 2.6, 7.7 Hz), 1.64 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 166.3, 145.6, 134.1, 131.7, 129.6, 128.6, 127.4, 126.9, 124.8, 113.9, 78.0, 76.5, 59.8, 58.4, 57.1, 52.6, 51.7, 14.3; IR (KBr) 3200, 2950, 1640, 1600, 1580, 1530, 1350, 1180, 1130, 990 cm^{-1}; HRMS (CI) Calc. for $C_{20}H_{19}NO_3Cl_4$ $[M+H]^+$, 462.020; Found, 462.021.

(1S,3aS,4S,7S,7aS)-4,5,6,7-tetrachloro-8,8-dimethoxy-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-ol (16): To a stirred solution of compound **7** (50 mg, 0.14 mmol) in acetonitrile (2 mL), was added BF_3-Et_2O (59 mg, 0.42 mmol) at 0 ^oC temperature. After 45 minutes the reaction mixture was quenched with ice (2 g). The organic compound was extracted with ethyl acetate (3x6mL), the combined organic layers were washed with saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography to obtain colorless crystalline compound **16**. R_f (30% Ethyl acetate in hexane) 0.5, mp 125 ^oC, yield 64% (32 mg, 0.089 mmol); ^1H NMR (400 MHz, $CDCl_3$) δ 5.40 (s, 1H), 4.36 (s, 1H), 3.67 (dd, 1H, *J* = 2.0, 7.4 Hz), 3.58 (s, 3H), 3.51(s, 3H), 2.98 (dd, 1H, *J* = 2.0, 7.4 Hz), 1.73 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 148.2, 130.4, 128.0, 125.7, 115.3, 78.9, 78.34, 78.25, 60.6, 60.4, 53.4, 52.5, 14.9; IR (KBr) 3200, 2980, 1610, 1440, 1260, 1130, 990, 810 cm^{-1}; HRMS (DCI) Calc. for $C_{13}H_{14}O_3Cl_4$ $[M\text{-}Cl]^+$, 323.001; Found, 323.003.

N-((1R,2R,3aS,4S,7S,7aS)-4,5,6,7-tetrachloro-8,8-dimethoxy-2-methyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoinden-1-yl)acetamide (17): To a stirred solution of substrate **13** (30 mg, 0.075 mmol) in ethyl acetate (2 mL) was added PtO_2 (2 mg, 0.009 mmol). The reaction mixture was stirred under hydrogen balloon over a period of 8 h then filtered through silica pad and washed with ethyl acetate (10 mL). The solvent was removed under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography to afford the pure solid compound **17** in excellent yield. R_f (40% Ethyl acetate in hexane) 0.4, colorless solid compound, mp 203-204 ^oC, yield 90% (27mg, 0.068 mmol); ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (bs, 1H), 3.55 (s, 3H), 3.50 (s, 3H), 3.1 (t, 1H, *J* = 8.8 Hz), 2.90 (t, 1H, *J* = 8.8 Hz), 2.00 (s, 3H), 1.96-1.90 (m, 2H), 0.98-0.84 (m, 2H), 0.92 (d, 3H, *J* = 4.9 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 170.1, 129.9,

115.4, 77.6, 77.3, 58.1, 56.8, 52.5, 51.7, 51.2, 42.1, 31.7, 23.2, 16.4; IR (KBr) 3320, 2990, 1650, 1610, 1560, 1450, 1320, 1195, 990, 780 cm^{-1}; HRMS (DCI) Calc. for $C_{15}H_{19}NO_3Cl_4$ $[M-Cl]^+$, 366.043; Found, 366.040.

(1R,3aR,4S,7S,7aR)-2,3,3a,7a-tetrachloro-4-methyl-3a,4,7,7a-tetrahydrospiro[4,7-methanoindene-1,2'-oxiran]-5(6H)-one (18): To the homogeneous solution of substrate **5** (100 mg, 0.32 mmol) in MeOH-THF (1:1), was added freshly prepared solution of diazomethane. The reaction mixture was cooled to -16 ^oC. After 24 hrs, excess diazomethane was quenched with few drops of glacial acetic acid. The solvent was removed under reduced pressure at room temperature. The crude reaction mixture was purified by silica gel column chromatography to furnish the colorless solid material along with starting material. R_f (10% Ethyl acetate in hexane) 0.5, colorless crystalline solid, mp 110 ^oC, yield 99% (52 mg, 0.158 mmol, 50% conversion); ^1H NMR (400 MHz, $CDCl_3$) δ 3.43 (d, 1H, *J* = 4.6 Hz), 3.25 (d, 1H, *J* = 4.9 Hz), 2.88 (d, 1H, *J* = 5.2 Hz), 2.55 (dd, 1H, *J* = 1.7, 4.6 Hz), 2.5 (d, 1H, *J* = 4.9 Hz), 2.3 (dd,1H, *J* = 5.4, 13.4 Hz), 1.70 (dd, 1H, *J* = 1.4, 11.6 Hz), 1.37 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 135.6, 130.2, 84.0, 79.9, 68.4, 65.2, 53.2, 46.8, 42.6, 40.4, 13.2; IR (KBr) 2930, 1754, 1623, 1514, 1208, 854, 710 cm^{-1}; Anal. Calc. for $C_{12}H_{10}O_2Cl_4$: C, 43.94; H, 3.07. Found: C, 43.75; H, 2.91.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Copies of ^{1}H and ^{13}C NMR spectra, HRMS and crystallographic data in CIF format].

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