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Papers

Asymmetric induction in copper (I)-catalyzed intramolecular [2 + 2] photocycloaddition: Synthesis of enantiopure cyclobutane derivatives

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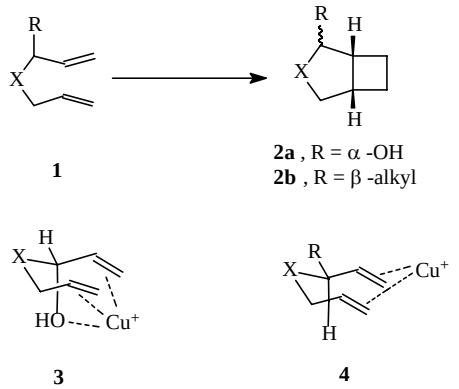
A simple approach for asymmetric induction in copper (I)-catalyzed intramolecular [2 + 2] photocycloaddition of 1,6-dienes, where asymmetric catalysis or chiral auxiliaries have been inefficient, has been developed using the concept of chirality transfer from the readily available 2,3-di-O-cyclohexylidine–(*R*)-(+)-glyceraldehyde to produce enantiopure oxa-bicyclo[3.2.0]heptane derivatives. A novel anion-induced cleavage of the tetrahydrofuran ring in these oxa-bicyclo[3.2.0]heptane derivatives has led to a convenient access to the synthetically useful *cis*-1,2-disubstituted cyclobutanes in enantiomerically pure form.

Keywords: Asymmetric synthesis, catalysis, cyclobutane, ether cleavage, photocycloaddition

IPC Code : Int. Cl.[8] C07C

The copper (I)-catalyzed intramolecular [2+2] photocycloaddition[1] reaction of 1,6-dienes is an extremely useful synthetic tool in organic synthesis. Photocycloaddition of 1,6-diene derivatives **1** proceeds stereoselectively to produce bicyclo[3.2.0]heptane derivatives **2** (**Scheme I**). The electronic and steric nature of the substituents at C-3 influences[2] the stereochemical outcome of this reaction to a great extent. It is well established that photocycloaddition requires prior formation of a Cu(I)-olefin complex such as **3** or **4** where the diene acts as a bidentate ligand. If one of the substituents at C-3 is a hydroxyl group such as the diene **1** (R=OH), photocycloaddition takes place through a tri-coordinated Cu (I) complex **3** to produce the bicyclo[3.2.0]heptane **2a** in which the OH group occupies an *endo* position.



1 — **2a** , R = α -OH; **2b** , R = β -alkyl

3 — **4**

Scheme I

On the other hand, if the substituent (R) at C-3 in the diene **1** is an alkyl group, photocycloaddition proceeds through the Cu (I) complex **4** rather than the sterically crowded Cu (I) complex with the alkyl group in *endo* position. This results in the formation of the bicyclo[3.2.0]heptane **2b** in which the alkyl group occupies an *exo* position. Due to these interesting characteristics, this reaction was used[3,4] as the key step in the synthesis of natural products and useful building blocks.

In spite of the great synthetic utility of Cu (I) catalyzed [2 + 2] photocycloaddition, its asymmetric version has been of little success. Langer and Mattay[5] investigated Cu (I) complex of several chiral bidentate ligands. They observed that such chiral Cu (I) complexes not only reduce significantly the rate of cycloaddition but also fails to induce asymmetry in the product. With only oxazoline ligands photoadducts were obtained with an enantiomeric excess of <5%. In an alternative approach[5], Cu (I)-catalyzed photocycloaddition of the esters of 1,6-heptadien-3-ol with a variety of chiral carboxylic acids as chiral auxiliary led to cyclobutanes with ee of 4-15% only. This necessitates the development of a new approach for asymmetric induction in copper (I)-catalyzed [2+2] photocycloaddition. As part of the continued interest[4] in Cu (I)-catalyzed [2+2] photocycloaddition reactions, herein is reported[6], a simple general solution to the problem of asymmetric induction in Cu (I)-catalyzed intramolecular [2+2]

photocycloaddition reactions leading to the synthesis of both enantiomers of oxa-bicyclo[3.2.0]heptanes.

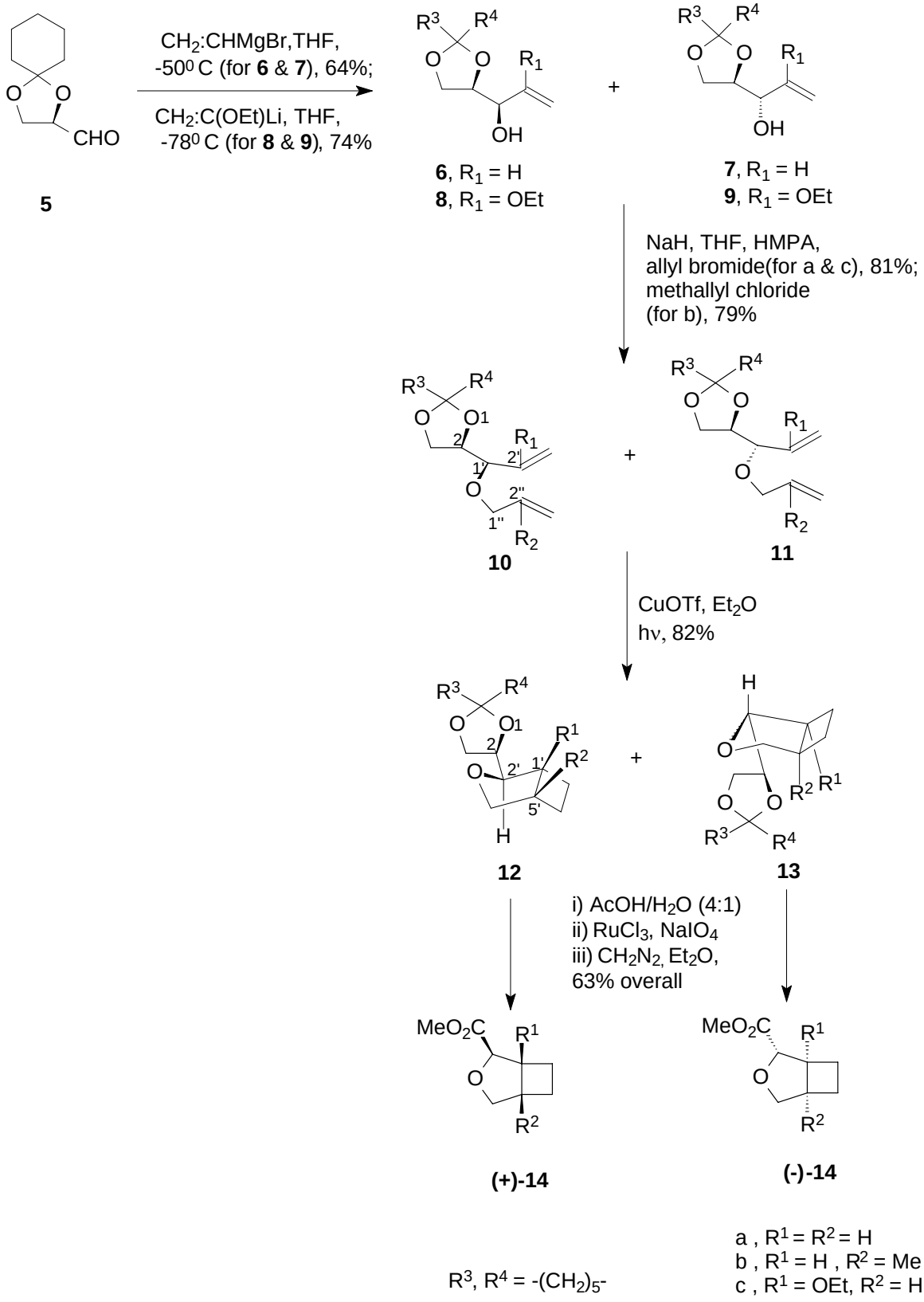
Results and Discussion

The present approach relies on the principle of chirality transfer that involves generation of new chiral centres in a chirally pure starting material followed by destruction of the original chiral center in the product. For the present investigation 2,3-di-O-cyclohexylidine-(*R*)-(+)-glyceraldehyde **5** (ref. 7) is chosen as the chiral adjuvant. The aldehyde functionality of the glyceraldehyde derivative **5** was elaborated to the 1,6-dienes in such a way to have the ketal unit at C-3 as photoaddition of such dienes are known to proceed stereoselectively. The dienes were prepared as delineated in **Scheme II**. Reaction of the aldehyde **5** with vinyl magnesium bromide afforded an inseparable mixture of the carbinols **6** and **7** in 64% yield in *ca.* 3:2 ratio. The assignment of stereochemistry to the isomers **6** and **7** is based on transformation to a compound of known absolute configuration as described. This mixture was then allylated with allyl bromide to produce a mixture of the corresponding allyl ethers **10a** and **11a** in 81% yield in about the same ratio (3:2). With methallyl chloride, the carbinols **6** and **7** gave the dienes **10b** and **11b** in 78% yield. For preparation of the dienes **10c** and **11c**, the aldehyde **5** was allowed to react with ethoxy vinyl lithium to produce a mixture of the carbinols **8** and **9** in 74% yield in a ratio of *ca.* 7:3. The mixture of the carbinols **8** and **9** were then allylated to produce a mixture of the dienes **10c** and **11c** in 81% yield, the ratio being the same.

With the dienes in hand, attention was focussed on their photocycloaddition. Irradiation of an ether solution of the mixture of the dienes **10a** and **11a** in the presence of copper(I)trifluoromethane sulfonate (CuOTf) as catalyst led to smooth cycloaddition to produce a mixture of the cyclobutane derivative **12a** and its C-2 epimer **13a**. Column chromatography of the crude product mixture led to isolation of the pure oxabicyclo[3.2.0]heptane **12a** and **13a** in 51% and 31% yields respectively. The ratio of the isolated yields of the photoadducts indicates that the photoadduct **12a** arose from the diene **10a** while **13a** arose from the diene **11a**. The *syn* stereochemical assignment of the C-2 substituents with the C-1 and C-5 hydrogens in the photoadducts **12a** and **13a** is based on analogy to the formation of the *exo* adduct **2b** from photocycloaddition of 3-alkyl-1,6-dienes **1** (R = alkyl)[2]. Similarly, irradiation of the mixture of the dienes **10b** and **11b** afforded the oxa-bicyclo[3.2.0]heptanes **12b** and **13b** in 48% and 34% yields respectively while irradiation of the diene mixture **10c** and **11c** gave the pure cyclobutane derivatives **12c** and **13c** in 53% and 29% yields respectively.

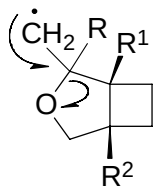
Attention was next focussed on destruction of the chirality present in the starting chiral adjuvant located at C-2 of the oxa-bicyclo[3.2.0]heptanes. This inolves acid induced deketalisation of the photoadducts to afford the corresponding diols. The diols thus obtained without isolation were oxidatively cleaved by RuO_4 to produce the corresponding carboxyclic acids which were then converted to the methyl esters. Thus, the adduct **12a** gave the methyl ester (+)-**14a**, $[\alpha]_D^{25}$ = +16.9° (*c* 1.38, $CHCl_3$) in 63% yield while its diastereoisomeric photoadduct **13a** gave the methyl ester with identical spectroscopic properties but specific rotation, $[\alpha]_D^{25}$ = -17.6° (*c* 1.39, $CHCl_3$), almost equal but opposite to that of the methyl ester **14a**. Thus, the methyl esters obtained from the diastereoisomeric photoadducts **12a** and **13a** bear an enantiomeric relationship with each other. In a similar fashion the diastereoisomeric cyclobutane pairs **12b** and **12c** afforded (+)- and (-) enantiomers of the structure **14b** while the diastereoisomeric pairs **12c** and **13c** gave the (+)- and (-) enantiomers of the cyclobutane derivative **14c**. The enantiomeric nature of the methyl esters **14** obtained from the diastereoisomeric pairs **12** and **13** was confirmed by measurement of CD spectra of the methyl esters **14c** obtained from **12c** and **13c**. The oxa-bicyclo[3.2.0]heptanes formed in this way are enantiomerically pure as the allylic chiral center (C-3) of the enantiomerically pure dienes **10** and **11** generated from the glyceraldehyde derivative **5** is still present in the oxa-bicyclo[3.2.0]heptanes **14**. The synthesis of both enantiomers of oxa-bicyclo[3.2.0]heptane derivatives using 2,3-di-O-cyclohexylidine (*R*)-(+)-glyceraldehyde **5** as chiral inducing agent is noteworthy as the enantiomer (*S*)-(-)-**5** is not readily available.

To extend the scope of this protocol the possibility of transforming the oxabicyclo[3.2.0]heptanes to *cis*-1,2-disubstituted cyclobutanes was considered. This is possible only if fragmentation of the relatively inert tetrahydrofuran ring present in them could be achieved. It was anticipated that generation of a radical **15** or an anion **16** might trigger fragmentation


CH2:CHMgBr,THF,
-50° C (for 6 & 7), 64%;
CH2:C(OEt)Li, THF,
-78° C (for 8 & 9), 74%
5
6, R1 = H
8, R1 = OEt
7, R1 = H
9, R1 = OEt
NaH, THF, HMPA,
allyl bromide(for a & c), 81%;
methallyl chloride
(for b), 79%
10
11
CuOTf, Et2O
hν, 82%
12
13
i) AcOH/H2O (4:1)
ii) RuCl3, NaIO4
iii) CH2N2, Et2O,
63% overall
(+)-14
(-)-14
R3, R4 = -(CH2)5-
a , R1 = R2 = H
b , R1 = H , R2 = Me
c , R1 = OEt, R2 = H

Scheme II

of the tetrahydrofuran ring. Toward this end, the lithium enolate generated from the ester (+)-**14c** was methylated to produce exclusively the *exo* methylated product **17** (**Scheme III**). The *exo* stereochemical assignment to the product **17** follows from alkylation of the enolate from the less hindered *exo* face. The ester **17** was then reduced with $LiAlH_4$ to provide the alcohol **18** in 89% yield. Transformation of the alcohol **18** to the corresponding bromide or xanthate, probable procursors for the radical **15**, could not be achieved. Wolff-Kishner reduction of aldehyde group to methyl is known to proceed through a carban-



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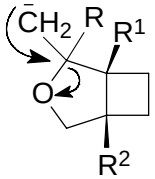


16

ionic intermediate. Thus, it was anticipated that the aldehyde **19** could be a precursor for the anion equivalent to **16**. Swern oxidation of the alcohol **18** afforded the aldehyde **19** in 65% yield. The aldehyde **19**, when subjected to Wolff-Kishner conditions, underwent smooth fragmentation to deliver the disubstituted cyclobutane **22** in 54% yield. This fragmentation protocol is found to be a general one. The enolate of **14c** was alkylated with benzyl bromide to give the product **20**. $LiAlH_4$ reduction of the ester **20** followed by Swern oxidation provided the aldehyde **21**. Attempted Wolff-Kishner reduction of the aldehyde **21** afforded the ring cleaved product **24**. The product **24** appears to arise from isomerization of the intially formed olefin **23**. Similarly, the enolate of (-)-**14b** was alkylated with MeI to lead to a diastereoisomeric mixture (2:5) of the esters **25**. $LiAlH_4$ reduction of this ester **25** followed by Swern oxidation gave the aldehyde **26**. Attempted Wolff-Kishner reduction effected smooth cleavage of the tetrahydrofuran ring to provide the known cyclobutane derivative **27**. As far as is known, the present protocol for the fragmentation of tetrahydrofuran rings is unprecedented[8]. The transformation of ent-**14**, which arises from the carbinol **7**, to the cyclobutane derivative **27** of known[9a] absolute configuration establishes the stereochemistry of the carbinol **7**.

cis-1,2-Disubstituted cyclobutane derivatives obtained in this way are of considerable synthetic use. For example, the cyclobutane derivative **27** $[\alpha]_D^{25}$ –4.1° (*c* 0.9, $CHCl_3$) has already been transformed to (–) grandisol **28** (ref. 9) by one-carbon homologation. On the other hand, the cyclobutane derivative **22**, when treated with Dowex-50, smoothly rearranged to the known cyclopentanone **29** $[\alpha]_D^{25}$ –63° (*c* 0.8, $CHCl_3$), an intermediate in the synthesis of the insect repellent β-necrodol **30**.

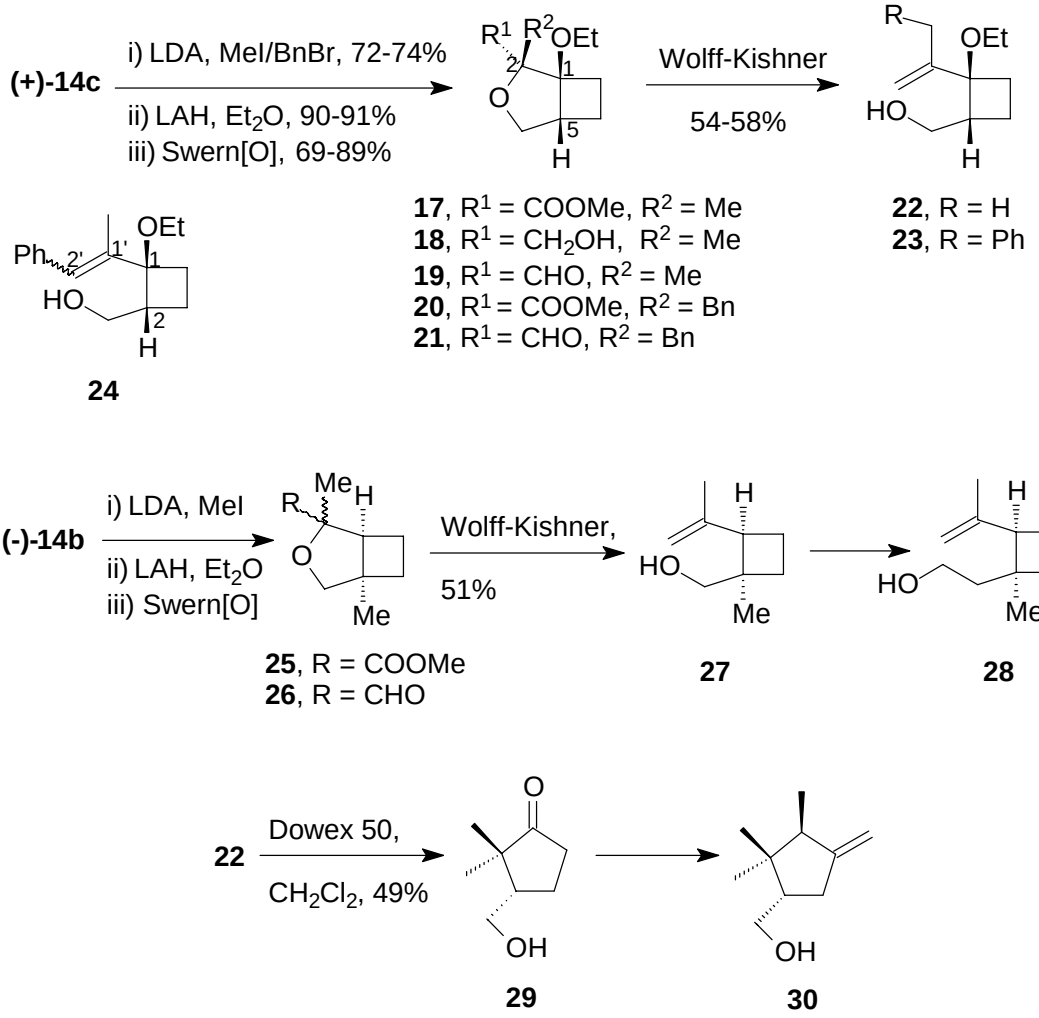
In conclusion, a simple approach for asymmetric induction in intramolecular Cu(I)-catalyzed [2+2] photocycloaddition reaction has been developed where asymmetric catalysts or chiral auxiliaries were inefficient. A combination of this sequence with the new protocol developed for the cleavage of tetrahyhydrofuran rings present in oxa-bicyclo[3.2.0]heptanes, resulted in the synthesis of useful *cis*-1,2-disubstituted cyclobutanes in enantiomerically pure form.

Experimental Section

All reactions were carried out under an atmosphere of N_2. A usual work-up involves extraction of the reaction mixture with diethyl ether, washing of organic extracts with brine, drying over anhydrous Na_2SO_4 and removal of solvent at reduced pressure. Column chromatography was performed on silica gel (60-120 mesh). Petroleum refers to the fraction of petroleum ether b.p. 60-80°C. IR spectra were recorded in thin film. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 and 75 MHz respectively. Elemental analyses were carried out at the microanalytical laboratory of this department.

Preparation of the dienes 10a-c and 11a-c.

(2*R*)-2-(1*R*-Allyloxyallyl)-1, 4-dioxa-spiro[4.5]-decane 10a and (2*R*)-2-(1*S*-Allyloxyallyl)-1,4-dioxa-spiro[4.5]decane 11a. To a magnetically stirred solution of the aldehyde **5** (2.4 g, 14.12 mmole) in dry THF (50 mL) at –50°C was added dropwise a solution of vinylmagnesium bromide [prepared from Mg (1.35 g, 56.47 mmole) and vinyl bromide (6 g, 56.47 mmole) in THF (25 mL)]. After complete addition the reaction mixture was stirred at that temperature for 1 h. Then it was allowed to attain RT slowly and stirred at that temperature for 1 h. The reaction mixture was cooled to 0°C and quenched by adding saturated NH_4Cl solution (7 mL). Usual work-up of the reaction mixture with ether followed by



Scheme III

column chromatography using ether-petroleum (1:9) as eluent afforded an inseparable mixture of the allyl alcohols **6** and **7** (1.8 g, 64%) in a *ca.* 3:2 ratio. ^{1}H NMR ($CDCl_3$): δ (for both isomers) 1.34 (m, 2H), 1.52 (br s, 4H), 1.58 (br s, 4H), 2.63 (br s, 1H), 3.70-4.21 (m, 4H), 5.16 (d, *J* = 10.59, 1H), 5.31 (d, *J* = 17.40 Hz, 1H), 5.68-5.84 (m, 1H); ^{13}C NMR ($CDCl_3$): δ (for major isomer) 24.1 (CH_2), 24.4 (CH_2), 25.4 (CH_2), 35.1 (CH_2), 36.7 (CH_2), 65.8 (CH_2), 74.6 (CH), 78.6 (CH), 110.7 (C), 118.1 (CH_2), 136.6 (CH); δ (for minor isomer) 24.1 (CH_2), 24.3 (CH_2), 25.5 (CH_2), 35.0 (CH_2), 36.5 (CH_2), 64.8 (CH_2), 72.3 (CH), 78.1 (CH), 110.3 (C), 117.0 (CH_2), 136.4 (CH). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.65; H, 9.15. Found: C, 66.39; H, 8.77%.

To a magnetically stirred suspension of NaH (0.65 g, 13.63 mmole, 50% suspension in oil), freed from adhering oil by repeated washing with petroleum ether, was added dropwise a solution of the mixture of the alcohols **6** and **7** (1.8 g, 9.09 mmole) in THF (15 mL) under N_2 atmosphere. The mixture was gently refluxed for 2h and then cooled to RT, and to it was added HMPA (2 mL) followed by allyl bromide (0.94 mL, 10.90 mmole). After refluxing for 2 h, the reaction mixture was cooled to RT and quenched by adding cold water (10 mL). Usual work-up of the reaction mixture followed by column chromatography of the crude product using ether-petroleum (1:19) as eluent afforded an inseparable mixture of the allyl ethers **10a** and **11a** in about the same ratio (3:2) as a colorless oil (1.75 g, 81%). ^{1}H NMR ($CDCl_3$): δ (for both diastereoisomers) 1.33-1.46 (m, 2H), 1.55-1.69 (m, 8H), 3.7-4.1 (m, 6H), 5.13-5.33 (m, 4H), 5.70-5.89 (m, 2H); ^{13}C NMR ($CDCl_3$): δ (for major isomer)

24.3 (CH_2), 24.4 (CH_2), 25.5 (CH_2), 35.3 (CH_2), 36.6 (CH_2), 66.4 (CH_2), 70.1 (CH_2), 77.3 (CH), 81.4 (CH), 110.4 (C), 117.4 (CH_2), 119.5 (CH_2), 135.1 (CH), 135.8 (CH); δ (for minor isomer) 24.2 (CH_2), 25.5 (CH_2), 25.5 (CH_2), 35.3 (CH_2), 36.6 (CH_2), 65.8 (CH_2), 70.0 (CH_2), 77.4 (CH), 81.6 (CH), 110.6 (C), 117.3 (CH_2), 120.0 (CH_2), 134.7 (CH), 135.2 (CH). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.36. Found: C, 70.15; H, 8.94%.

(2*R*)-2-[1*R*-(2-Methylallyloxy)-allyl]-1, 4-dioxa-spiro[4.5]decane 10b and (2*R*)-2-[1*S*-(2-Methylallyloxy)-allyl]-1, 4-dioxa-spiro[4.5]decane 11b. Following the above procedure of allylation for **10a** and **10b**, the allyl alcohol **6** and **7** (2.0 g, 10.10 mmol) was reacted with methallyl chloride (1.2 mL, 12.12 mmol) to afford a mixture of the dienes **10b** and **11b** (1.98g, 78%) as a colorless oil in about 3:2 ratio. ^{1}H NMR ($CDCl_3$): δ (for both diastereoisomers) 1.32-1.38 (m, 2H), 1.57-1.59 (m, 8H), 1.77 (s, CH_3 of the major isomer), 1.79 (s, CH_3 of the minor isomer), 3.67-4.14 (m, 6H), 4.85-4.94 (m, 2H,), 5.23-5.29 (m, 2H), 5.58-5.76 (m, 1H); ^{13}C NMR ($CDCl_3$): δ (for major isomer) 19.9 (CH_3), 24.2 (CH_2), 25.5 (CH_2), 35.2 (CH_2), 36.6 (CH_2), 66.4 (CH_2), 72.9 (CH_2), 77.7 (CH), 81.1 (CH), 110.3 (C), 112.7 (CH_2), 119.4 (CH_2), 135.8 (CH), 142.3 (C); δ (for minor isomer) 19.8 (CH_3), 24.3 (CH_2), 25.5 (CH_2), 35.3 (CH_2), 36.6 (CH_2), 65.7 (CH_2), 72.6 (CH_2), 77.4 (CH), 81.1 (CH), 110.5 (C), 112.7 (CH_2), 119.9 (CH_2), 134.6 (CH), 142.5 (C). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.40; H, 9.59. Found: C, 71.54; H, 9.14%.

(2*R*)-2-(1*S*-Allyloxy-2-ethoxy-allyl)-1, 4-dioxa-spiro[4.5]decane 10c and (2*R*)-2-(1*R*-allyloxy-2-ethoxy-allyl)-1,4-dioxa-spiro[4.5]decane 11c. To a magnetically stirred solution of ethyl vinyl ether (2.86 g, 39.7 mmol) in anhydrous THF (25 mL) under argon atomsphere, was added *t*-BuLi (15.8 mL, 23.82 mmol) dropwise. After complete addition, the bath temperature was slowly raised to –20°C and stirred for 30 minutes at that temperature. The reaction mixture was again cooled to –78°C and to it a solution of the aldehyde **5** (2.7 g, 15.88 mmole) in THF (15 mL) was added dropwise. After complete addition the bath temperature was slowly raised to RT and stirring was continued for 1 h. The reaction mixture was then cooled to –20°C and quenched by addition of saturated aqueous NH_4Cl solution (5 mL). Usual work-up of the reaction mixture afforded a mixture of the carbinols **8** and **9** (2.84 g, 74%) in a *ca.*7:3 ratio. b.p. 125-130°C (0.5 mm Hg). ^{1}H NMR ($CDCl_3$): δ (for both diastereoisomers) 1.26 (t, J = 7 Hz, CH_3 of the minor isomer), 1.27 (t, J = 7.1 Hz, CH_3 of the major isomer), 1.34-1.37 (m, 2H), 1.56 (br s, 4H), 1.61 (br s, 4H), 3.68-3.80 (m, 3H), 3.86-4.03 (m, 4H), 4.18-4.27 (m, 2H); ^{13}C NMR ($CDCl_3$): (for major isomer) δ 14.7 (CH_3), 24.1 (CH_2), 24.3 (CH_2), 25.5 (CH_2), 35.0 (CH_2), 36.8 (CH_2), 63.4 (CH_2), 64.7 (CH_2), 72.2 (CH), 77.4 (CH), 83.2 (CH_2), 110.2 (C), 160.9 (C); δ (for minor isomer) 14.7 (CH_3), 24.2 (CH_2), 25.5 (CH_2), 35.1 (CH_2), 36.8 (CH_2), 64.1 (CH_2), 66.4 (CH_2), 74.3 (CH), 77.8 (CH), 83.4 (CH_2), 110.6 (C), 160.3 (C).

Following the above procedure for allylation of the carbinols **6** and **7**, the mixture of the carbinols **8** and **9** (1.8 g, 7.42 mmole) was allylated with allyl bromide (1.08 g, 8.90 mmole) to afford a mixture of the dienes **10c** and **11c** as a colorless oil (1.7 g, 81%) in about 3:2 ratio. b.p. 95-98°C (0.5 mm Hg); ^{1}H NMR ($CDCl_3$): δ (for both diastereoisomers) 1.26 (t, J = 7 Hz, CH_3 for minor isomer), 1.27 (t, J = 7.0 Hz, CH_3 of major isomer), 1.56-1.58 (m, 4H), 1.60-1.61 (m, 6H), 3.71 (q, J = 7.3 Hz, 2H), 3.72 (q, J = 6.7 Hz, 2H,), 3.86-4.26 (m, 8H), 5.12-5.31 (m, 2H), 5.80-5.92 (m, 1H); ^{13}C NMR ($CDCl_3$): δ (for major isomer), 14.7 (CH_3), 24.3 (CH_2), 24.4 (CH_2), 25.6 (CH_2), 35.5 (CH_2), 36.6 (CH_2), 63.4 (CH_2), 66.1 (CH_2), 70.4 (CH_2), 76.3 (CH), 80.7 (CH), 85.3 (CH_2), 110.1 (C), 117.4 (CH_2), 135.1 (CH), 159.1 (C); δ (for minor isomer) 14.6 (CH_3), 24.2 (CH_2), 24.3 (CH_2), 24.4 (CH_2), 25.6 (CH_2), 35.5 (CH_2), 36.7 (CH_2), 63.4 (CH_2), 66.1 (CH_2), 70.1 (CH_2), 77.4 (CH), 82.1 (CH), 85.4 (CH_2), 110.5 (C), 117.5 (CH_2), 135.2 (CH), 159.1 (C). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 67.86; H, 9.33%.

Photocycloaddition of the dienes 10a-c and 11a-c.

(2*R*)-2-[(1*R*,2*R*,5*S*)-3-oxabicyclo[3.2.0]hept-2-yl]-1,4-dioxa-spiro[4.5]decane 12a and (2*R*)-2-[(1*S*, 2*R*, 5*R*)-3-oxabicyclo[3.2.0]hept-2-yl)]-1, 4-dioxa-spiro-[4.5]decane 13a. A magnetically stirred solution of the dienes **10a** and **11a** (1.75 g, 7.35 mmole) in diethyl ether (250 mL) containing CuOTf (0.2 mmole) under Ar atmosphere was irradiated internally with a Hanovia 450W medium pressure mercury vapor lamp through a water cooled immersion well for 6 h. The reaction mixture was then washed successively with ice-cold aqueous NH_4OH (2×10 mL) and water (2×10 mL) and dried. Evaporation of ether followed by column chromatography (diethyl ether-petroleum 1/19) of the residual mass afforded

the cyclobutane derivatives **12a** (0.96 g, 51%). $[\alpha]_D^{25}$ + 15.1° (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.25 (br s, 2H), 1.53 (br s, 2H), 1.54 (br s, 2H), 1.56 (br s, 2H), 1.57 (br s, 2H), 1.68-1.80 (m, 2H), 2.11-2.23 (m, 2H), 2.97-3.03 (m, 2H), 3.74-3.89 (m, 5H), 4.02 (dd, *J* = 3.0, 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 23.9 (CH_2), 24.2 (CH_2), 24.4 (CH_2), 24.4 (CH_2), 25.6 (CH_2), 35.2 (CH_2), 36.9 (CH_2), 39.5 (CH), 41.1 (CH), 67.6 (CH_2), 75.0 (CH_2), 75.9 (CH), 87.6 (CH), 110.1 (C). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.36. Found: C, 70.23; H, 9.02% and **13a** (0.58 g, 31%). $[\alpha]_D^{25}$ –11.3° (*c* 1.65, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.32-1.40 (m, 2H), 1.50-1.52 (m, 2H), 1.55-1.58 (m, 2H), 1.60 (br s, 2H), 1.61 (br s, 2H), 1.75-1.79 (m, 2H), 2.15-2.21 (m, 2H), 2.69-2.75 (m, 1H), 2.84-2.92 (m, 1H), 3.62 (dd, *J* = 5.9, 6.4 Hz, 1H), 3.78 (dd, *J* = 1.9, 8.9 Hz, 1H), 3.88-3.97 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 24.2 (CH_2), 24.2 (CH_2), 24.3 (CH_2), 24.4 (CH_2), 25.5 (CH_2), 35.3 (CH_2), 36.6 (CH_2), 39.8 (CH), 41.4 (CH), 66.0 (CH_2), 75.2 (CH_2), 77.9 (CH), 86.8 (CH), 110.4 (C).

(2*R*)-2-[(1*R*,2*R*,5*S*)-5-methyl-3-oxabicyclo-[3.2.0]-hept-2-yl]-1,4-dioxa-spiro[4.5]-decane (12b) and (2*R*)-2-[(1*S*, 2*R*, 5*R*)-5-methyl-3-oxabicyclo [3.2.0]-hept-2-yl]-1,4-dioxa-spiro[4.5]-decane (13b). Following the above procedure, photocycloaddition of the dienes **10b** and **11b** (1.6 g, 6.35 mmole) gave the adducts **12b** (0.77 g , 48%). $[\alpha]_D^{25}$ +15.4° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.25 (s, 3H), 1.33-1.38 (m, 2H), 1.54 (br s, 4H), 1.61 (br s, 4H), 1.63-1.98 (m, 2H), 2.15-2.19 (m, 2H), 2.52-2.58 (m, 1H), 3.48 (d, *J* = 8.7 Hz, 1H), 3.69-3.80 (m, 3H), 3.94-4.05 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 20.8 (CH_2), 23.0 (CH_3), 24.2 (CH_2), 24.4 (CH_2), 25.6 (CH_2), 30.4 (CH_2), 35.1 (CH_2), 36.8 (CH_2), 46.2 (CH), 47.0 (C), 67.5 (CH_2), 76.6 (CH), 80.3 (CH_2), 88.3 (CH), 110.4 (C) and **13b** (0.54g, 33%). $[\alpha]_D^{25}$ –22.7° (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.19 (s, 3H), 1.26-1.33 (m, 2H), 1.45-1.51 (m, 4H), 1.54-1.64 (m, 6H), 1.73-1.77 (m, 1H), 1.93-1.97 (m, 1H), 2.09-2.20 (m, 1H), 3.53-3.71 (m, 3H), 3.82-3.98 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 21.0 (CH_2), 22.9 (CH_3), 24.2 (CH_2), 24.4 (CH_2), 25.5 (CH_2), 30.5 (CH_2), 35.3 (CH_2), 36.6 (CH_2), 47.0 (C), 47.1 (CH), 66.0 (CH_2), 76.4 (CH), 80.6 (CH_2), 87.5 (CH), 110.4 (C). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.40; H, 9.59. Found: C, 71.57; H, 9.06%.

2*R*-2-[(1*S*, 2*S*, 5*R*)-1-Ethoxy-3-oxabicyclo[3.2.0]-hept-2-yl]-1,4-dioxa-spiro[4.5]decane 12c and 2*R*-2-[(1*R*, 2*R*, 5*S*)-1-Ethoxy-3-oxabicyclo[3.2.0]hept-2-yl]-1,4-dioxa-spiro[4.5]decane 13c. Following the above procedure, photocycloaddition of the dienes **10c** and **11c** (1.7 g, 6.03 mmole) afforded the adducts **12c** (0.9 g, 53%). R_f 0.39 (ethyl acetate-petroleum 1:4); $[\alpha]_D^{25}$ + 12.9° (*c* 1.38, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.18 (t, *J* = 7.0 Hz, 3H), 1.35-1.45 (m, 2H), 1.54-1.60 m, 4H), 1.61-1.69 (m, 4H), 1.98-2.10 (m, 3H), 2.34-2.42 (m, 1H), 2.99-3.06 (m, 1H), 3.47-3.66 (m, 3H), 3.93-4.05 (m, 4H), 4.33 (q, *J* = 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 15.5 (CH_3), 18.9 (CH_2), 23.8 (CH_2), 24.0 (CH_2), 25.1 (CH_2), 25.8 (CH_2), 34.7 (CH_2), 36.2 (CH_2), 43.7 (CH), 60.0 (CH_2), 66.1 (CH_2), 73.4 (CH_2), 73.6 (CH), 86.2 (C), 87.4 (CH), 109.0 (C) and its C_2 epimer **13c** (0.49 g, 29%). R_f = 0.33 (ethyl acetate-petroleum ether 1:4); $[\alpha]_D^{25}$ = -23.1° (*c* 0.9 in $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.16 (t, *J* = 6.9 Hz, 3H), 1.25-1.67 (m, 10H), 1.95-2.01 (m, 3H), 2.04-2.43 (q, *J* = 8.4 Hz, 1H), 3.07-3.14 (m, 1H), 3.48-3.85 (m, 5H), 4.08-4.15 (m, 2H), 4.29 (q, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 15.5 (CH_3), 18.4 (CH_2), 23.7 (CH_2), 23.9 (CH_2), 25.1 (CH_2), 34.6 (CH_2), 36.1 (CH_2), 42.3 (CH), 60.1 (CH_2), 65.7 (CH_2), 73.3 (CH_2), 74.8 (CH), 86.9 (C), 89.6 (CH), 109.2 (C). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 67.72; H, 8.94%.

(1*R*,2*R*,5*S*)-3-oxabicyclo[3.2.0]heptane-2-carboxylic acid methyl ester (+)-14a. A solution of the photoadduct **12a** (0.5 g, 2.1 mmole) in aqueous acetic acid (90%, 5 mL) was stirred at RT for 24 h. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with NaOH solution (20%, 3×5 mL) to make it alkaline (*p*H paper). The organic layer was dried and concentrated to afford the corresponding diol (300 mg). To this diol was added carbon tetrachloride (6 mL), acetonitrile (6 mL) and water (12 mL), sodium metaperiodate (1.27 g, 5.9 mmol) and $RuCl_3.3H_2O$ (4 mg). The mixture was allowed to stir at RT for 1.5 h. The white precipitate formed was then filtered off. The filtrate was extracted with ethyl acetate (3×10 mL). The ethyl acetate extract was washed with saturated $NaHCO_3$ solution (3×3 mL). The combined $NaHCO_3$ washing, on cooling (ice-bath), was acidified with hydrochloric acid (6 *N*). The reaction mixture was then extracted with ethyl acetate (3×5 mL). The organic extract was washed with brine (2×3 mL) and dried. Removal of the solvent under reduced pressure gave a liquid which was then treated with an ethereal solution of diazomethane. Removal of ether followed by filtration through a short column of neutral alumina afforded the methyl ester (+)-**14a**

as a colorless liquid (200 mg, 63%). $[\alpha]_D^{25}$ +16.9° (*c* 1.38, $CHCl_3$); IR (thin film): 1747 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.66-1.80 (m, 2H), 2.05-2.23 (m, 2H), 2.91-2.96 (m, 1H), 3.04-3.08 (m, 1H), 3.63 (s, 3H), 3.86 (d, *J* = 8.9 Hz, 1H), 3.94 (dd, *J* = 5.6, 9.1 Hz, 1H), 4.36 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 23.9 (CH_2), 24.0 (CH_2), 38.8 (CH), 43.4 (CH), 52.1 (CH_3), 74.7 (CH_2), 83.8 (CH), 173.4 (C). Anal. Calcd for $C_8H_{12}O_3$: C, 61.56; H, 7.75. Found: C, 61.21; H, 7.49%.

(1*S*,2*S*,5*R*)-3-oxabicyclo[3.2.0]heptane-2-carboxylic acid methyl ester (-)-14a. Following the above procedure the photoadduct **13a** (300 mg, 1.26 mmol) was converted to the methyl ester (-)-**14a** (124 mg, overall 63%). $[\alpha]_D^{25}$ –17.6° (*c* 1.39, $CHCl_3$); IR and NMR spectra were identical with those of (+)-**14a**.

(1*R*,2*R*,5*S*)-5-Methyl-3-oxabicyclo[3.2.0]-heptane-2-carboxylic acid methyl ester (+)-14b. Following the above procedure for synthesis of methyl ester **14a**, the photoadduct **12b** (0.5 g, 1.98 mol) afforded the methyl ester (+)-**14b** as a colorless liquid (210 mg, 63%). $[\alpha]_D^{25}$ + 24.5° (*c* 1.22, $CHCl_3$); IR (thin film): 1747 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.22 (s, 3H), 1.67-1.85 (m, 2H), 1.96-2.05 (m, 1H), 2.16-2.25 (m, 1H), 2.64 (q, *J* = 4.6 Hz, 1H), 3.68 (d, *J* = 8.7 Hz, 1H), 3.69 (s, 3H), 3.85 (d, *J* = 8.8 Hz, 1H), 4.38 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.3 (CH_2), 22.2 (CH_3), 29.9 (CH_2), 45.8 (C), 48.4 (CH), 51.6 (CH_3), 80.5 (CH_2), 83.7 (CH), 173.1 (C). Anal. Calcd for $C_9H_{14}O_3$: C, 63.52; H, 8.29. Found: C, 63.16; H, 7.81%.

(1*S*,2*S*,5*R*)-5-Methyl-3-oxabicyclo[3.2.0]-heptane-2-carboxylic acid methyl ester (-)-14b. Following the above procedure, the photoadduct **13b** (200 mg, 0.79 mmole) was converted to the methyl ester **(-)-14b** (85 mg, overall 63%). $[\alpha]_D^{25}$ –23.8° (*c* 1.28, $CHCl_3$). IR and NMR spectra were identical with those of (+)-**14b**.

(1*S*,2*R*,5*R*)-1-Ethoxy-3-oxabicyclo[3.2.0]-heptane-2-carboxylic acid methyl ester (+)-14c. Following the above procedure for synthesis of methyl ester **14a**, the photoadduct **12c** (0.5 g, 1.77 mmole) afforded the methyl ester **(+)-14c** as a colorless liquid (220 mg, 63%). $[\alpha]_D^{25}$ = + 36.4° (*c* 1.42, $CHCl_3$); IR (thin film): 1750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.13 (t, *J*= 7.1 Hz, 3H), 1.47-1.54 (m, 1H), 2.01-2.17 (m, 2H), 2.41-2.52 (m, 1H), 3.00 (dd, *J*= 6, 14.5 Hz, 1H), 3.53 (m, 2H), 3.72 (s, 3H), 3.81 (d, *J*= 8.8 Hz, 1 H), 4.42 (dd, *J*= 5.5, 9.0 Hz, 1H), 4.50 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 15.9 (CH_3), 18.4 (CH_2), 27.8 (CH_2), 43.5 (CH), 52.0 (CH_3), 61.2 (CH_2), 75.2 (CH_2), 86.3 (CH), 89.4 (C), 171.9 (C) . Anal. Calcd for $C_{10}H_{16}O_4$: C,59.99; H, 8.06. Found: C, 59.61; H, 8.14%.

(1*R*,2*S*,5*S*)-1-Ethoxy-3-oxabicyclo[3.2.0]-heptane-2-carboxylic acid methyl ester (-)-14c. Following the above procedure, the photoadduct **13c** (200 mg, 0.71 mmole) was converted to the methyl ester **(-)-14c** (90 mg, 63%). $[\alpha]_D^{25}$ –35.7° (*c* 1.53, $CHCl_3$). IR and NMR spectra were identical with those of (+)-**14c**.

(1*S*,2*S*,5*R*)-1-Ethoxy, 2-methyl-3-oxabicyclo-[3.2.0]heptane-2-carboxylic acid methyl ester 17. A solution of the methyl ester **(+)-14c** (320 mg, 1.6 mmol) in THF (3 mL) was added dropwise to a magnetically stirred solution of LDA [prepared from diisopropylamine (0.52 g, 5.1 mmole) in anhydrous THF (3 mL) and *n*-BuLi (1.5 mL, 2.4 mmole, 1.6 M in hexane)] at –78° C under Ar. The reaction mixture was then slowly warmed to –30°C and stirred at that temperature for 1.5 h. The reaction mixture was again cooled to –78°C and to it HMPA (0.5 mL) followed by methyl iodide (0.32 mL,5.1 mmole) were added dropwise. The reaction mixture was allowed to attain RT and stirred for 18 h. After quenching with saturated aqueous ammonium chloride solution (1 mL), the reaction mixture was extracted with ether (3×10 mL) and dried. Removal of solvent under reduced pressure afforded a liquid which was chromatographed using ether-petroleum (3:17) as eluent to afford the ester **17** (246 mg, 72%). $[\alpha]_D^{25}$ + 8.4° (*c* 0.8, $CHCl_3$); IR (thin film): 1734 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.16 (t, *J* = 6.9 Hz, 3H), 1.34 (s, 3H), 1.52-1.57 (m, 1H), 1.79-1.88 (m, 1H), 1.94-2.04 (m, 1H), 2.18-2.24 (m, 1H), 2.74-2.77 (m, 1H), 3.44 (q, *J* = 7 Hz, 1H), 3.58 (q, *J* = 7 Hz, 1H), 3.73 (d, *J* = 7.1 Hz, 1H), 3.74 (s, 3H), 3.88 (dd, *J* = 5.0, 9.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 16.1 (CH_3), 18.0 (CH_2), 18.7 (CH_3), 25.6 (CH_2), 44.4 (CH), 52.5 (CH_3), 60.3 (CH_2), 70.5 (CH_2), 88.7 (C), 88.8 (C), 173.9 (C). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.68; H, 8.47. Found: C, 61.33; H, 8.09%.

[(1*S*, 2*S*, 5*R*)-1-Ethoxy, 2-methyl-3-oxabicyclo-[3.2.0]hept-2-yl]-methanol 18. A solution of the ester **17** (250 mg, 1.17 mmole) in diethyl ether (2 mL) was added to a stirred suspension of $LiAlH_4$ (53 mg, 1.4 mmole) in diethyl ether at 0°C. Stirring was continued for 1h at RT. To the ice cooled reaction mixture was added sequentially, water (0.5 mL), 15% aq. NaOH solution (0.5 mL) and water (1.6 mL). The resulting suspension was stirred for 15 min. The precipitated white solid was removed by filtration. Evaporation of

the solvent followed by column chromatography using ether-petroleum (1:4) as eluent afforded the alcohol **18** (198 mg, 91%) as a colorless viscous liquid. $[\alpha]_D^{25}$ – 7.2° (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.16(s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.44-1.51 (m, 1H), 1.63 (br s, 1H), 2.05-2.16 (m, 2H), 2.36-2.39 (m, 2H), 2.81-2.83 (m, 1H), 3.42 (q, *J* = 8.5 Hz, 2H), 3.63 (dd, *J* = 2.6, 9.4 Hz, 2H), 3.76 (d, *J* = 11.1 Hz, 1H), 3.92 (dd, *J* = 5.3, 9.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 16.2 (CH_3), 17.3 (CH_3), 19.2 (CH_2), 23.8 (CH_2), 44.1 (CH), 60.3 (CH_2), 67.6 (CH_2), 70.3 (CH_2), 84.6 (C), 89.3 (C). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.16; H, 9.38%.

(1*S*, 2*S*, 5*R*)-1-Ethoxy, 2-methyl-3-oxabicyclo-[3.2.0]heptane-2-carbaldehyde 19. To a stirred solution of oxalyl chloride (0.24 mL, 2.71 mmole) in dichloromethane (1.5 mL) cooled to –70°C under Ar was added a solution of DMSO (0.4 mL, 5.65 mmole) in dichloromethane (1.5 mL). After stirring for 15 min, a solution of the alcohol **18** (210 mg, 1.13 mmole) in dichloromethane (1.5 mL) was added to it. The reaction mixture was stirred for 45 min. Triethylamine (1.26 mL, 9.04 mmole) was added and the reaction mixture was allowed to attain RT. The mixture was poured into water (2 mL) and extracted with dichloromethane (3×3 mL) . The organic extract was washed with aqueous HCl (2 mL, 10%), brine (1 mL), and dried. Removal of the solvent afforded a yellow liquid which was chromatographed using ether-petroleum (1:9) as eluent to afford the aldehyde **19** (0.14 g, 69%). $[\alpha]_D^{25}$ + 68.3° (*c* 0.9, $CHCl_3$); IR (thin film): 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.14 (t, *J* = 6.8 Hz, 3H), 1.16 (s, 3 H), 1.57-1.61 (m, 1H), 1.98-2.20 (m, 3H), 2.76-2.83 (m, 1H), 3.38 (q, *J* = 7.1 Hz, 2H), 3.78 (d, *J* = 9.5 Hz, 1H), 3.95 (dd, *J* = 5.1, 9.5 Hz, 1H), 9.77 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 15.9 (CH_3), 15.9 (CH_3), 18.5 (CH_2), 24.4 (CH_2), 45.1 (CH), 60.4 (CH_2), 71.1 (CH_2), 89.2 (C), 90.1 (C), 204.7 (CH). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.20; H, 8.75. Found: C, 64.73; H, 8.37%.

(1*S*,2*R*,5*R*)-2-Benzyl, 1-ethoxy-3-oxabicyclo-[3.2.0]heptane-2-carboxylic acid methyl ester 20. Following the above procedure for methylation of the ester **14c**, the lithium enolate of the methyl ester **14c** (260 mg, 1.3 mmole) was alkylated with benzyl bromide (0.23 mL, 7.9 mmole) to afford the benzylated ester **20** (280 mg, 74%) as a colorless oil. $[\alpha]_D^{25}$ +3.5° (*c* 0.8, $CHCl_3$); IR (thin film): 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.27 (t, *J* = 7.0 Hz, 3H), 1.56-1.60 (m, 1H), 1.80-1.89 (m, 1H), 2.02-2.07 (m, 1H), 2.28-2.35 (m, 1H), 2.87-2.90 (m, 1H), 3.06 (d, *J* = 5.3 Hz, 2H), 3.54-3.60 (m, 1H), 3.62 (s, 3H), 3.79-3.86 (m, 2H,), 4.08 (dd, *J* = 4.9, 9.5 Hz, 1H), 7.14-72.5 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 15.7 (CH_3), 17.6 (CH_2), 25.6 (CH_2), 36.0 (CH_2), 44.1 (CH), 51.7 (CH_3), 60.1 (CH_2), 70.0 (CH_2), 88.9 (C), 91.9 (C), 126.4 (CH), 127.9 (CH), 129.9 (CH), 136.6 (C), 172.1 (C). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.33; H, 7.64. Found: C, 70.69; H, 7.47%.

(1*S*,2*R*,5*R*)-2-Benzyl, 1-ethoxy-3-oxabicyclo-[3.2.0]heptane-2-carbaldehyde 21. Following the above procedure for reduction of the methyl ester **17**, the benzylated ester **20** (280 mg, 0.96 mmole) was reduced to the corresponding alcohol (230 mg, 90%). $[\alpha]_D^{25}$ + 6.7° (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.17 (t, *J* = 7.0 Hz, 3H), 1.39-1.43 (m, 1H), 1.89 (br s, 1H), 1.98-2.05 (m, 2H), 2.17-2.20 (m, 1H), 2.33-2.38 (m, 1H), 2.73 (d, *J* = 14.8 Hz, 1H), 2.82 (d, *J* = 14.5 Hz, 1H), 3.35-3.55 (m, 3H), 3.58-3.64 (m, 2H), 4.05 (dd, *J* = 5.6, 9.5 Hz, 1H), 7.09-7.25 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 15.8 (CH_3), 19.2 (CH_2), 24.1 (CH_2), 33.5 (CH_2), 43.5 (CH), 60.4 (CH_2), 62.0 (CH_2), 70.2 (CH_2), 85.5 (C), 90.5 (C), 126.0 (CH), 127.8 (CH), 130.6 (CH), 138.0 (C). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.26; H, 8.45. Found: C, 72.93; H, 8.48%.

Following the above procedure for synthesis of aldehyde **19**, the alcohol (230 mg, 0.88 mmole) was oxidised to the corresponding aldehyde **21** (180 mg, 79%). $[\alpha]_D^{25}$ + 2.8° (*c* 0.8, $CHCl_3$). IR (thin film): 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.27 (t, *J* = 7.0 Hz, 3H), 1.61-1.66 (m, 1H), 2.02-2.18 (m, 2H), 2.21-2.27 (m, 1H), 2.90-2.92 (m, 1H), 3.06 (s, 2H), 3.51 (q, *J* = 7.1 Hz, 1H), 3.63 (q, *J* = 7.0 Hz, 1H), 3.87 (d, *J* = 9.6 Hz, 1H), 4.14 (dd, *J* = 5.3, 9.5 Hz, 1H), 7.13-7.27 (m, 5H), 9.64 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 15.5 (CH_3), 18.3 (CH_2), 24.2 (CH_2), 34.5 (CH_2), 44.6 (CH), 60.2 (CH_2), 70.6 (CH_2), 89.6 (C), 92.5 (C), 126.4 (CH), 128.0 (CH), 130.3 (CH), 136.0 (C), 205.4 (CH).

[(1*R*, 2*S*)-2-Ethoxy-2-isopropenyl-cyclobutyl]-methanol 22. A mixture of the aldehyde **19** (140 mg, 0.76 mmole), hydrazine hydrate (2.49 mL, 99%), hydrazine dihydrochloride (0.64 g) and diethylene glycol (9 mL) was heated to 120°C for 1.5 h under N_2. The reaction mixture was then cooled to 70°C and potassium hydroxide pellet (1.17 g) was added. The temperature was gradually raised to 210°C and maintained at that temperature for 1 h. On cooling to RT the mixture was poured into ice cold water (15 mL). The organic material in it was extracted with ether (3×10 mL). Removal of ether followed by

column chromatography of the residual liquid using ether-petroleum (1:4) afforded **22** (70 mg, 54%) as a colorless liquid. $[\alpha]_D^{25}$ -109.1° (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.15 (t, *J* = 7.1 Hz, 3H), 1.33-1.38 (m, 1H), 1.73 (s, 3H), 1.87-1.97 (m, 3H), 2.12-2.28 (m, 1H), 2.54-2.57 (m, 1H), 3.02-3.07 (m, 1H), 3.18-3.23 (m, 1H), 3.44 (dd, *J* = 6.7, 11.2 Hz, 1H), 3.60 (dd, *J* = 7.1, 11.1 Hz, 1H), 4.98 (s, 1H), 5.10 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 18.0 (CH_3), 19.1 (CH_2), 21.6 (CH_3), 29.0 (CH_2), 50.4 (CH), 60.0 (CH_2), 65.3 (CH_2), 86.4 (C), 116.1 (CH_2), 146.8 (C). Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H,10.65. Found: C, 70.24; H, 10.18%.

[(1*R*, 2*S*)-2-Ethoxy-2-(1-methyl-2-phenylvinyl)-cyclobutyl)-methanol 24. Following the above procedure for synthesis of compound **22**, aldehyde **21** (200 mg, 0.77 mmole) was subjected to Wolff-Kishner condition to afford the compound **24** (110 mg, 58%). $[\alpha]_D^{25}$ –9.8° (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.20 (t, *J* = 6.8 Hz, 3H), 1.26-1.50 (m, 2H), 1.80 (br s, 1H), 1.88 (s, 3H), 2.00-2.10 (m, 2H), 2.43-2.50 (m, 1H), 2.62-2.67 (m, 1H), 3.14 (q, *J* = 7.3 Hz, 1H), 3.15 (dd, *J* = 7.2, 10.8 Hz, 1H), 3.69 (d, *J* = 6.8, 10.8 Hz, 1H), 6.51 (s, 1H), 7.22-7.38 (m, 5H) ; ^{13}C NMR ($CDCl_3$): δ 14.8 (CH_3), 15.6 (CH_3), 16.9 (CH_2), 20.1 (CH_2), 48.3 (CH), 57.6 (CH_2), 63.0 (CH_2), 85.3 (C), 126.5 (CH), 127.4 (CH), 128.1 (CH), 128.9 (CH), 137.5 (C). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.60; H, 9.19%.

(1*S*,2*R*)-2,5-Dimethyl-3-oxabicyclo[3.2.0]heptane-2-carboxylic acid methyl ester 25. Following the above procedure for methylation of ester **14c**, the ester (-)-**14b** (230 mg, 1.35 mmole) was alkylated with methyl iodide (0.17 mL, 2.7 mmole) to afford the methyl ester **25** as an oil (170 mg, 68%). IR (thin film): 1734 cm^{-1}; ^1H NMR ($CDCl_3$): δ (for major isomer) 1.21 (s, 3H), 1.29 (s, 3H), 1.43-1.52 (m, 1H), 1.65-1.75 (m, 1H), 1.84-1.96 (m, 2H), 2.38-2.43 (m, 1H), 3.55 (d, *J* = 9.2 Hz, 1H), 3.68 (s, 3H), 3.89 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ (for major isomer) 17.7 (CH_2), 22.3 (CH_3), 23.6 (CH_3), 29.3 (CH_2), 45.4 (C), 51.9 (CH_3), 52.6 (CH), 78.7 (CH_2), 87.3 (C), 173.3 (C) and ^1H NMR ($CDCl_3$): δ (for minor isomer) 1.16 (s, 3H), 1.41 (s, 3H), 1.66-1.97 (m, 4H), 2.74-2.78 (m, 1H), 3.55 (d, *J* = 8.9 Hz, 1H), 3.70 (s, 3H), 3.84 (d, *J* = 9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ (for minor isomer) 15.2 (CH_2), 19.0 (CH_3), 22.9 (CH_3), 30.2 (CH_2), 45.9 (C), 50.5 (CH), 52.0 (CH_3), 79.9 (CH_2), 85.8 (C), 175.8 (C). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.20; H, 8.76. Found: C, 64.89; H, 8.27%.

(1*S*,5*R*)-2,5-Dimethyl-3-oxabicyclo[3.2.0]heptane-2-carbaldehyde 26. Following the above procedure for synthesis of aldehyde **19** the methyl ester (190 mg, 1.03 mmole) was reduced with $LiAlH_4$ to the corresponding alcohol (140 mg, 87%). ^1H NMR ($CDCl_3$): (mixture of two diastereoisomers) 1.10 (s, CH_3 of major isomer), 1.22 (s, CH_3 of minor isomer), 1.25 (s, CH_3 of major isomer) 1.73-2.02 (m, 4H), 2.17-2.21 (m, 1H), 3.36-3.58 (m, 2H), 3.66-3.75 (m, 2H); ^{13}C NMR ($CDCl_3$): δ (for major isomer), 15.0 (CH_2), 21.4 (CH_3), 23.5 (CH_3), 30.1 (CH_2), 46.5 (C), 51.5 (CH), 66.6 (CH_2), 77.7 (CH_2), 84.4 (C); ^{13}C NMR ($CDCl_3$): δ (for minor isomer), 15.1 (CH_2), 18.1 (CH_3), 23.1 (CH_3), 30.0 (CH_2), 46.5 (C), 49.0 (CH), 65.2 (CH_2), 77.4 (CH_2), 84.4 (C). This alcohol (180 mg, 1.15 mmole) was converted to the corresponding aldehyde **26** (110 mg, 62%) as a colorless liquid; IR (thin film): 1741 cm^{-1}; ^1H NMR ($CDCl_3$): (mixture of two diastereoisomers), δ 1.09 (s, CH_3 of minor isomer), 1.12 (s, CH_3 of major isomer), 1.20 (s, CH_3 of minor isomer), 1.23 (s, CH_3 of major isomer) 1.66-1.80 (m, 2H), 1.84-1.97 (m, 2H), 2.37-2.58 (m, 1H), 3.25 (d, *J* = 9.4 Hz, 1H), 3.59 (d, *J* = 9.2 Hz, 1H), 3.74 (d, *J* = 9.4 Hz, 1H), 3.92 (d, *J* = 9.2 Hz, 1H), 9.49 (s, 1H), 9.72 (s, 1H); ^{13}C NMR ($CDCl_3$): δ (for major isomer) 15.8 (CH_2), 19.6 (CH_3), 23.4 (CH_3), 30.0 (CH_2), 46.2 (C), 52.3 (CH), 78.9 (CH_2), 89.0 (C), 203.9 (CH); ^{13}C NMR ($CDCl_3$): δ (for minor isomer) 14.4 (CH_2), 19.6 (CH_3), 22.1 (CH_3), 29.6 (CH_2), 46.8 (C), 52.3 (CH), 79.3 (CH_2), 89.0 (C), 204.1 (CH).

[(1*R*, 2*R*)-2-isopropenyl-1-methyl-cyclobutyl]-methanol 27. Following the above procedure for synthesis of the cyclobutane **22**, the aldehyde **26** (80 mg, 0.519 mmole) was converted to the cyclobutane derivative **27** (37 mg, 51%). $[\alpha]_D^{25}$ – 4.1° (C 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.22 (s, 3H), 1.76 (s, 3H), 1.80-1.85 (m, 2H), 2.00-2.07 (m, 2H), 2.62 (t, *J* = 9.3 Hz, 1H), 3.47 (d, *J* = 11.4 Hz, 1H), 3.59 (d, *J* = 11.5 Hz, 1H), 4.76 (s, 1H), 4.86 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 15.9 (CH_3), 19.2 (CH_3), 25.5 (CH_2), 27.1 (CH_2), 49.7 (CH), 67.3 (CH_2), 82.2 (C), 109.4 (CH_2), 146.3 (C).

(*S*)-3-Hydroxymethyl-2, 2-dimethylcyclopentanone 29. A solution of the alcohol **22** (30 mg, 0.176 mmol) in dichloromethane (0.5 mL) was stirred with Dowex-50 (20 mg) at RT for 24 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (0.2 mL), extracted with ether (3×3 mL) and

dried (anhyd. Na_2SO_4). Evaporation of solvent under vacuum followed by column chromatography of the residual liquid using ether-petroleum ether (1:3) as eluent afforded cyclopentanone **29** (12 mg, 49%) as colorless liquid. IR (thin film): 1732 cm^{-1}; $[\alpha]_D^{25}$ –63° (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.93 (s, 3H), 1.13 (s, 3H), 1.70-1.75 (m, 2H), 2.03-2.15 (m, 4H), 3.66-3.85 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 18.5 (CH_3), 22.8 (CH_2), 24.5 (CH_3), 30.1 (CH_2), 49.6 (CH), 56.2 (C), 64.1 (CH_2), 216.4 (C).

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