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 oxabicyclo[3.2.0]heptane derivatives. A novel anion-induced cleavage of the tetrahydrofuran ring in these oxabicyclo[3.2.0]heptane derivatives has led to a convenient access to the synthetically useful \(c\text{is}\)-1,2-disubstituted cyclobutanes in enantiomerically pure form.

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

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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 tricoordinated Cu (I) complex \(3\) to produce the bicyclo[3.2.0]heptane \(2a\) in which the OH group occupies an \(endo\) position.

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 \(exo\) 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.
photocycloaddition reactions leading to the synthesis of both enantiomers of oxabicyclo[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-cyclohexyldine-(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 carbinalds 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 carbinalds 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 carbinalds 8 and 9 in 74% yield in a ratio of ca. 7:3. The mixture of the carbinalds 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 stereochemoassignement 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 oxabicyclo[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 oxabicyclo[3.2.0]heptanes. This involves 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 carboxylic acids which were then converted to the methyl esters. Thus, the adduct 12a gave the methyl ester (+)-14a, \([\alpha]_D^{25} = +16.9^\circ\) (c 1.38, CHCl\(_3\)) in 63% yield while its diastereoisomeric photoadduct 13a gave the methyl ester with identical spectroscopic properties but specific rotation, \([\alpha]_D^{25} = -17.6^\circ\) (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 oxabicyclo[3.2.0]heptanes formed in this way are enantiomerically pure as the allylic chiral center (C-3) of the enantiomercially pure dienes 10 and 11 generated from the glyceraldehyde derivative 5 is still present in the oxabicyclo[3.2.0]heptanes 14. The synthesis of both enantiomers of oxabicyclo[3.2.0]heptane derivatives using 2,3-di-O-cyclohexyldine (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...
\[
\text{CH}_2\text{CHMgBr, THF, -50}^\circ\text{C (for 6 & 7), 64%; CH}_2\text{C(OEt)Li, THF, -78}^\circ\text{C (for 8 & 9), 74%}
\]

\[
\begin{align*}
\text{NaH, THF, HMPA, allyl bromide (for a & c), 81%; methallyl chloride (for b), 79%}
\end{align*}
\]

\[
\text{CuOTf, Et}_2\text{O, hv, 82%}
\]

\[
\begin{align*}
i) \text{AcOH/H}_2\text{O (4:1)} \\
ii) \text{RuCl}_3, \text{NaIO}_4 \\
iii) \text{CH}_2\text{N}_2, \text{Et}_2\text{O, 63% overall}
\end{align*}
\]

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C} \\
\text{(+)-14} & \quad \text{(-)-14}
\end{align*}
\]

\[
\begin{align*}
R^3, R^4 &= -(\text{CH}_2)_5^- \\
\]

\begin{align*}
a, R^1 &= R^2 = H \\
b, R^1 &= H, R^2 = \text{Me} \\
c, R^1 &= \text{OEt}, R^2 = H
\end{align*}

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 LiAlH4 to provide the alcohol 18 in 89% yield. Transformation of the alcohol 18 to the corresponding bromide or xanthate, probable precursors for the radical 15, could not be achieved. Wolff-Kishner reduction of aldehyde group to methyl is known to proceed through a carbanionic 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. LiAlH4 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 initially formed olefin 23. Similarly, the enolate of (-)-14b was alkylated with MeI to lead to a diastereoisomeric mixture (2:5) of the esters 25. LiAlH4 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 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 [α]D 25 −4.1° (c 0.9, CHCl3) has already been transformed to (−) granisol 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 [α]D 25 −63° (c 0.8, CHCl3), 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 tetrahydrofuran 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 N2. A usual work-up involves extraction of the reaction mixture with diethyl ether, washing of organic extracts with brine, drying over anhydrous Na2SO4 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 13C NMR spectra were recorded in CDCl3 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.**

(2R)-2-(1R- Allyloxyallyl)-1, 4-dioxaspiro[4.5]-decane 10a and (2R)-2-(1S- Allyloxyallyl)-1,4-dioxaspiro[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 NH4Cl solution (7 mL). Usual work-up of the reaction mixture with ether followed by
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$_3$): $\delta$ (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$_3$): $\delta$ (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); $\delta$ (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 (1:9) 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$_3$): $\delta$ (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$_3$): $\delta$ (for major isomer)
24.3 (CH₂), 24.4 (CH₂), 25.5 (CH₂), 35.3 (CH₂), 36.6 (CH₂), 66.4 (CH₂), 70.1 (CH₂), 77.3 (CH), 81.4 (CH), 110.4 (C), 117.4 (CH₂), 119.5 (CH₂), 135.1 (CH), 135.8 (CH); δ (for minor isomer) 24.2 (CH₂), 25.5 (CH₂), 35.3 (CH₂), 36.6 (CH₂), 65.8 (CH₂), 70.0 (CH), 77.4 (CH), 81.6 (CH), 110.6 (C), 117.3 (CH₂), 120.0 (CH₂), 134.7 (CH), 135.2 (CH). Anal. Calcd for C₁₄H₂₂O₃: C, 70.56; H, 9.36. Found: C, 70.15; H, 8.94%.

(2R)-2-[1R-(2-Methylallyloxy)-allyl]-1, 4-dioxaspiro[4.5]decane 10b and (2R)-2-[1S-(2-Methylallyloxy)-allyl]-1, 4-dioxaspiro[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.

1H NMR (CDCl₃): δ (for both diastereoisomers) 1.32-1.38 (m, 2H), 1.57-1.59 (m, 8H), 1.77 (s, CH₃ of the major isomer), 1.79 (s, CH₃ 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); 13C NMR (CDCl₃): δ (for major isomer) 19.9 (CH₃), 24.2 (CH₂), 25.5 (CH₂), 35.2 (CH₂), 36.6 (CH₂), 66.4 (CH₂), 72.9 (CH₂), 77.7 (CH), 81.1 (CH), 110.3 (C), 112.7 (CH₂), 119.4 (CH₂), 135.8 (CH), 142.3 (C); δ (for minor isomer) 19.8 (CH₃), 24.3 (CH₂), 25.5 (CH₂), 35.3 (CH₂), 36.6 (CH₂), 65.7 (CH₂), 72.6 (CH₂), 77.4 (CH), 81.1 (CH), 110.5 (C), 112.7 (CH₂), 119.9 (CH₂), 134.6 (CH), 142.5 (C). Anal. Calcd for C₁₅H₂₄O₃: C, 71.40; H, 9.32. Found: C, 70.53; H, 9.41%.

(2R)-2-(1S-allyloxy-2-ethoxy-allyl)-1, 4-dioxaspiro[4.5]decane 10c and (2R)-2-(1S-allyloxy-2-ethoxy-allyl)-1,4-dioxaspiro[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 atmosphere, was added t-BuLi (15.8 mL, 23.82 mmol) 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 NH₄Cl 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). 1H NMR (CDCl₃): δ (for both diastereoisomers) 1.26 (t, J = 7 Hz, CH₃ of the minor isomer), 1.27 (t, J = 7.1 Hz, CH₃ 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); 13C NMR (CDCl₃): δ (for major isomer) 14.7 (CH₃), 24.1 (CH₂), 24.3 (CH₂), 25.5 (CH₂), 35.0 (CH₂), 36.8 (CH₂), 63.4 (CH₂), 64.7 (CH₂), 72.2 (CH), 77.4 (CH), 83.2 (CH₂), 110.2 (C), 160.9 (C); δ (for minor isomer) 14.7 (CH₃), 24.2 (CH₂), 25.5 (CH₂), 35.1 (CH₂), 36.8 (CH₂), 64.1 (CH₂), 66.4 (CH₂), 74.3 (CH), 77.8 (CH), 83.4 (CH₂), 110.6 (C), 160.3 (C).

Following the above procedure for allylation of the carbinols 6 and 7, the allyl alcohol 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); 1H NMR (CDCl₃): δ (for both diastereoisomers) 1.26 (t, J = 7 Hz, CH₃ of minor isomer), 1.27 (t, J = 7.0 Hz, CH₃ of major isomer), 1.56-1.58 (m, 4H), 1.60-1.61 (m, 4H), 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, 2H); 13C NMR (CDCl₃): δ (for major isomer), 14.7 (CH₃), 24.3 (CH₂), 24.4 (CH₂), 25.6 (CH₂), 35.5 (CH₂), 36.6 (CH₂), 63.4 (CH₂), 66.1 (CH₂), 70.4 (CH₂), 76.3 (CH), 80.7 (CH), 85.3 (CH₂), 110.1 (C), 117.4 (CH₂), 135.1 (CH), 159.1 (C); δ (for minor isomer) 14.6 (CH₃), 24.2 (CH₂), 24.3 (CH₂), 24.4 (CH₂), 25.6 (CH₂), 35.5 (CH₂), 36.7 (CH₂), 63.4 (CH₂), 66.1 (CH₂), 70.1 (CH₂), 77.4 (CH), 82.1 (CH), 85.4 (CH₂), 110.5 (C), 117.5 (CH₂), 135.2 (CH), 159.1 (C). Anal. Calcd for C₁₅H₂₄O₃: C, 68.06; H, 9.28. Found: C, 67.86; H, 9.33%.

Photocycloaddition of the dienes 10a-c and 11a-c. (2R)-2-[(1R,2R,5S)-3-oxabicyclo[3.2.0]hept-2-yl]-1,4-dioxaspiro[4.5]decane 12a and (2R)-2-[(1S,2R,5R)-3-oxabicyclo[3.2.0]hept-2-yl]-1,4-dioxaspiro[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 NH₄OH (2× 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%). \( [\alpha]_D^{25} + 15.1^o \) (c 1.5, CHCl3); \(^1H\) NMR (CDCl3): \( \delta \) 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), 4.00 (dd, \( J = 3.0, 6.0 \text{ Hz}, 1H \)); \(^13C\) NMR (CDCl3): \( \delta \) 23.9 (CH3), 24.2 (CH2), 24.4 (CH2), 24.6 (CH2), 25.6 (CH2), 35.2 (CH2), 36.9 (CH2), 39.5 (CH), 41.1 (CH), 67.6 (CH2), 75.0 (CH2), 75.9 (CH), 87.6 (CH), 110.1 (C). Anal. Calcd for C14H22O3: C, 70.56%; H, 9.36%. Found: C, 71.40; H, 9.59.

The combined NaHCO3 washing, on cooling (ice-bath), was acidified with hydrochloric acid (6 N). The organic layer was washed with an ethereal solution of diazomethane. Removal of ether followed by filtration through a short column of neutral alumina afforded the methyl ester (+)-14a.

\((1R,2R,5S)-3\)-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 then extracted with ethyl acetate (20 mL) and washed with NaOH solution (20%, 3×5 mL) to make it alkaline (pH 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 RuCl3.3H2O (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 NaHCO3 solution (3×3 mL). The combined NaHCO3 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%). \([\alpha]_D^{25} +16.9^\circ\) (c 1.38, CHCl3); IR (thin film): 1747 cm\(^{-1}\); \(^1\)H NMR (CDCl3): \(\delta\) 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); \(^1\)C NMR (CDCl3): \(\delta\) 23.9 (CH2), 38.8 (CH), 43.4 (CH), 52.1 (CH2), 74.7 (CH3), 83.8 (CH), 173.4 (C). Anal. Calcd for C8H12O3: C, 61.56; H, 7.75. Found: C, 61.21; H, 7.49%.

\((1S,2S,5R)-3\)-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%). \([\alpha]_D^{25} -17.6^\circ\) (c 1.39, CHCl3); IR and NMR spectra were identical with those of \((+)-14a\).

\((1R,2R,5S)-5\)-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%). \([\alpha]_D^{25} +24.5^\circ\) (c 1.22, CHCl3); IR (thin film): 1747 cm\(^{-1}\); \(^1\)H NMR (CDCl3): \(\delta\) 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); \(^1\)C NMR (CDCl3): \(\delta\) 20.3 (CH2), 22.2 (CH3), 29.9 (CH2), 45.8 (C), 48.4 (CH), 51.6 (CH3), 80.5 (CH2), 83.7 (CH), 173.1 (C). Anal. Calcd for C10H16O4: C, 61.68; H, 8.29. Found: C, 63.16; H, 7.81%.

\((1S,2S,5R)-5\)-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%). \([\alpha]_D^{25} -23.8^\circ\) (c 1.28, CHCl3). IR and NMR spectra were identical with those of \((+)-14b\).

\((1S,2R,5R)-1\)-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%). \([\alpha]_D^{25} +36.4^\circ\) (c 1.42, CHCl3); IR (thin film): 1750 cm\(^{-1}\); \(^1\)H NMR (CDCl3): \(\delta\) 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, 1H), 4.42 (dd, \(J = 5.5, 9.0\) Hz, 1H), 4.50 (s, 1H); \(^1\)C NMR (CDCl3): \(\delta\) 15.9 (CH3), 18.4 (CH2), 27.8 (CH2), 43.5 (CH), 52.0 (CH3), 61.2 (CH2), 75.2 (CH2), 86.3 (CH), 89.4 (C), 171.9 (C). Anal. Calcd for C10H18O4: C, 59.99; H, 8.06. Found: C, 59.61; H, 8.14%.

\((1R,2S,5S)-1\)-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%). \([\alpha]_D^{25} -35.7^\circ\) (c 1.53, CHCl3). IR and NMR spectra were identical with those of \((+)-14c\).

\((1S,2S,5R)-1\)-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%). \([\alpha]_D^{25} +8.4^\circ\) (c 0.8, CHCl3); IR (thin film): 1734 cm\(^{-1}\); \(^1\)H NMR (CDCl3): \(\delta\) 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); \(^1\)C NMR (CDCl3): \(\delta\) 16.1 (CH3), 18.0 (CH2), 18.7 (CH3), 25.6 (CH2), 44.4 (CH), 52.5 (CH2), 60.3 (CH2), 70.5 (CH2), 88.7 (C), 88.8 (C), 173.9 (C). Anal. Calcd for C11H18O4: C, 63.52; H, 7.47. Found: C, 63.13; H, 7.81%.

\((1S,2S,5R)-1\)-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 LiAlH4 (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% eq. 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. [α] D 25 − 7.2° (c 0.8, CHCl 3); 1H 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 (dd, J = 11.1 Hz, 1H), 3.92 (dd, J = 5.3, 9.4 Hz, 1H); 13C 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 16 O 3 : C, 65.20; H, 8.75%.

1H NMR (CDCl 3): 3.78 (d, J = 11.1 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), 7.14-7.25 (m, 5H); 13C 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 2), 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 25 O 4 : C, 70.33; H, 7.64. Found: C, 70.69; H, 7.47%.

(1S,2S,5R)-2-Benzyl, 1-ethoxy-3-oxabicyclo-[3.2.0]heptane-2-carboxylic acid methyl ester 20. Following the above procedure for reduction of the methyl ester 17, the benzylation ester 20 (280 mg, 0.96 mmole) was reduced to the corresponding alcohol (230 mg, 90%). [α] D 25 + 6.7° (c 1.1, CHCl 3). 1H 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); 13C NMR (CDCl 3): δ 15.8 (CH 2), 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 19 H 25 O 3 : C, 73.26; H, 8.45. Found: C, 72.93; H, 8.48%.

Following the above procedure for synthesis of alcohol 19, the alcohol (230 mg, 0.88 mmole) was oxidised to the corresponding aldehyde 21 (180 mg, 79%). [α] D 25 + 2.8° (c 0.8, CHCl 3). IR (thin film): 1738 cm −1 ; 1H 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); 13C 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).

[(1R, 2S)-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. [α]D
\textsuperscript{25} -109.1° (c 1.6, CHCl₃); \textsuperscript{1}H NMR (CDCl₃): 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); \textsuperscript{13}C NMR (CDCl₃): δ 18.0 (CH₂), 19.1 (CH₃), 21.6 (CH₃), 29.0 (CH₂), 50.4 (CH), 60.0 (CH₂), 65.3 (CH₃), 86.4 (C), 116.1 (CH₂), 146.8 (C). Anal. Calcd. for C\textsubscript{10}H\textsubscript{18}O₂: C, 77.60; H, 9.19%. Found: C, 64.89; H, 8.27%.

(1S,5R)-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 LiAlH₄ to the corresponding alcohol (140 mg, 87%). \textsuperscript{1}H NMR (CDCl₃): (mixture of two diastereoisomers) 1.10 (s, CH₃ of major isomer), 1.22 (s, CH₃ of minor isomer), 1.25 (s, CH₃ 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); \textsuperscript{13}C NMR (CDCl₃): δ (for major isomer), 15.0 (CH₂), 21.4 (CH₃), 23.5 (CH₃), 30.1 (CH₃), 46.5 (C), 51.5 (CH), 66.6 (CH₂), 77.7 (CH₂), 84.4 (C). \textsuperscript{13}C NMR (CDCl₃): δ (for minor isomer), 15.1 (CH₂), 18.1 (CH₃), 23.1 (CH₃), 30.0 (CH₃), 46.5 (C), 49.0 (CH), 65.2 (CH₂), 77.4 (CH₂), 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; \textsuperscript{1}H NMR (CDCl₃): (mixture of two diastereoisomers), δ 1.09 (s, CH₃ of minor isomer), 1.12 (s, CH₃ of major isomer), 1.20 (s, CH₃ of minor isomer), 1.23 (s, CH₃ of major isomer) 1.66-1.80 (m, 2H), 1.84-1.97 (m, 2H), 2.37-2.58 (m, 1H), 2.35 (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); \textsuperscript{13}C NMR (CDCl₃): δ (for major isomer) 15.8 (CH₂), 19.6 (CH₃), 23.4 (CH₄), 30.0 (CH₂), 46.2 (C), 52.3 (CH), 78.9 (CH₂), 89.0 (C), 203.9 (CH); \textsuperscript{13}C NMR (CDCl₃): δ (for minor isomer) 14.4 (CH₂), 19.6 (CH₃), 22.1 (CH₃), 29.6 (CH₂), 46.8 (C), 52.3 (CH), 79.3 (CH₂), 89.0 (C), 204.1 (CH).

(1R, 2S)-2,2-Dimethylcyclopropylcarboxylic 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; \textsuperscript{1}H NMR (CDCl₃): 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); \textsuperscript{13}C NMR (CDCl₃): δ (for major isomer) 17.7 (CH₂), 22.3 (CH₂), 23.6 (CH₃), 29.3 (CH₃), 45.4 (C), 51.9 (CH₃), 52.6 (CH), 78.7 (CH₂), 87.3 (C), 173.3 (C) and \textsuperscript{1}H NMR (CDCl₃): 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); \textsuperscript{13}C NMR (CDCl₃): δ (for minor isomer) 15.2 (CH₂), 19.0 (CH), 22.9 (CH₃), 30.2 (CH₂), 45.9 (C), 50.5 (CH), 52.0 (CH₂), 79.9 (CH₂), 85.8 (C), 175.8 (C). Anal. Calcd. for C\textsubscript{10}H\textsubscript{16}O₃: C, 65.20; H, 8.76. Found: C, 64.89; H, 8.27%.

(1S,2R)-2,5-Dimethyl-3-oxabicyclo[3.2.0]heptane-2-carboxylic acid methyl ester 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%). [α]D
\textsuperscript{25} -4.1° (C 0.9, CHCl₃); \textsuperscript{1}H NMR (CDCl₃): 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); \textsuperscript{13}C NMR (CDCl₃): δ 15.9 (CH₂), 19.2 (CH₂), 25.5 (CH₃), 27.1 (CH₂), 49.7 (CH), 67.3 (CH₂), 82.2 (C), 109.4 (CH), 146.3 (C).

(5S)-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 NaHCO₃ solution (0.2 mL), extracted with ether (3×3 mL) and
dried (anhyd. Na₂SO₄). 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; [α]D²⁵ –63° (c 0.9, CHCl₃); ¹H NMR (CDCl₃): 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); ¹³C NMR (CDCl₃): δ 18.5 (CH₃), 22.8 (CH₂), 24.5 (CH₂), 30.1 (CH₂), 49.6 (CH), 56.2 (C), 64.1 (CH₂), 216.4 (C).

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References
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