



# Intramolecular [2+2] photocycloaddition of 1,6-dienes incorporated in a furanose ring. Unusual formation of *cis-syn-cis* 6-oxatricyclo[6.2.0.0<sup>3,7</sup>]decanes

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Received 4 May 2001; revised 21 June 2001; accepted 28 June 2001

**Abstract**—Intramolecular [2+2] photocycloaddition of 1,6-dienes incorporated in a furanose ring either in the presence of a copper(I) catalyst or with a sensitizer led to the unusual formation of *cis-syn-cis* adducts. © 2001 Elsevier Science Ltd. All rights reserved.

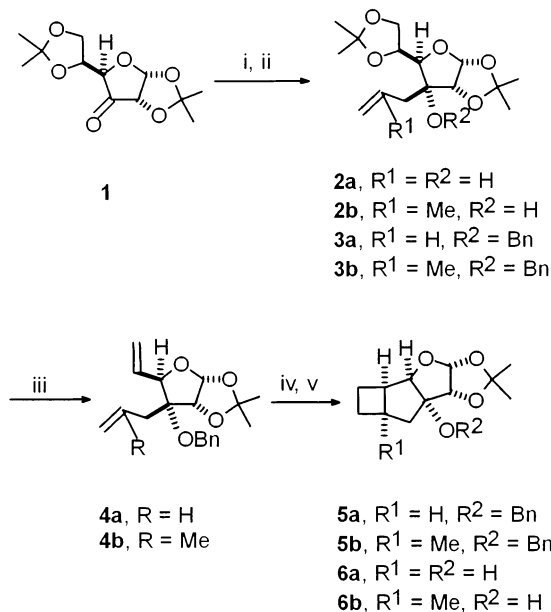
The [2+2] photocycloaddition reaction<sup>1</sup> offers an excellent stereoselective pathway for rapid access to systems of intractable complexity incorporating cyclobutanes. In general inter- and intramolecular [2+2] photocycloaddition of two alkenes leading to linearly arrayed tricyclic systems proceeds to produce the thermodynamically more stable *cis-anti-cis* adducts predominantly. A similar trend is also observed in ketene–olefin<sup>2</sup> and Diels–Alder<sup>3</sup> cycloadditions. In connection with a synthetic program we needed rapid construction of a linearly arrayed *cis-anti-cis* 4-5-5 tricyclic system in enantiomerically pure form. It appeared to us that an intramolecular [2+2] photocycloaddition of a 1,6-diene built in a furanosugar template would afford the desired *cis-anti-cis* 4-5-5 tricyclic system. While Diels–Alder<sup>4</sup> and 1,3-dipolar<sup>5</sup> cycloaddition reactions in furanosugar templates have occasionally been investigated, [2+2] photocycloaddition reactions in furanosugars have not been explored.<sup>6</sup> We now report the intramolecular [2+2] photocycloaddition of the dienes **4** and **11** incorporated in a furanosugar resulting in the unexpected formation of the thermodynamically less stable *cis-syn-cis* 4-5-5 linearly arrayed tricyclic structures.

4\_\_\_\_\_

**Keywords:** carbohydrates; cycloaddition; cyclobutanes; photochemistry; stereocontrol.

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The diene **4a** was prepared from the known ketone **1** as delineated in Scheme 1. Reaction of the ketone **1** with allyl bromide and Zn dust afforded the homoallylic



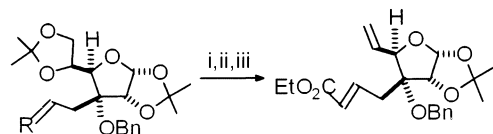
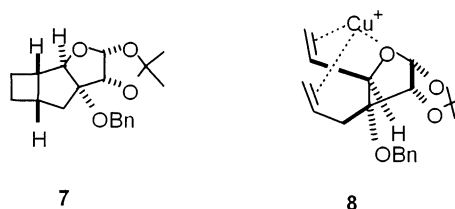
**Scheme 1.** Reagents and conditions: (i) Zn, CH<sub>2</sub>=CHCH<sub>2</sub>Br, rt, 70% (for **2a**); CH<sub>2</sub>=CH(Me)CH<sub>2</sub>MgCl, THF, rt, 70% (for **2b**); (ii) NaH, BnBr, THF, reflux, 2 h, 70–80%; (iii) (a) 75% aq. AcOH, rt, 12 h, (b) I<sub>2</sub>, PPh<sub>3</sub>, imidazole, PhMe, reflux, 2 h, 53–57%; (iv) *hν*, CuOTf, Et<sub>2</sub>O, 3.5 h, 72–77%; (v) 10% Pd–C, H<sub>2</sub>, MeOH, AcOH, HClO<sub>4</sub>, 80–85%.

alcohol **2a**<sup>7</sup> in 70% yield. The hydroxy group in the allylated product **2a** was protected to afford the benzyl ether **3a**.<sup>8</sup> The ether **3a** was converted to the diene **4a** in 53% yield using a two-step sequence involving selective deprotection of the 5,6-acetonide moiety followed by conversion<sup>9</sup> of the resulting diol to an olefin. When a solution of the diene **4a** in diethyl ether was irradiated in the presence of copper(I) trifluoromethane sulfonate (CuOTf)<sup>10</sup> as catalyst, smooth cycloaddition took place to afford a single adduct **5a** as a crystalline solid, mp 52°C in 73% yield.

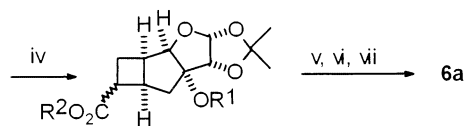
The gross structure of the photoadduct **5a** could be easily ascertained from its <sup>1</sup>H and <sup>13</sup>C NMR spectra. Preliminary information regarding the stereochemistry was obtained from the coupling constant between the C<sub>7</sub>-H and C<sub>8</sub>-H in the hydroxy compound **6a** obtained on removal of the benzyl group from the adduct **5a**. The C<sub>7</sub>-H appeared at δ 4.15 as a doublet with a coupling constant of 5.5 Hz. This coupling constant on comparison with those reported<sup>10</sup> for the proton α to the hydroxy group in a series of *exo* (*J*=4.5 Hz) and *endo* (*J*=6–8 Hz) 2-hydroxy bicyclo[3.2.0]heptanes indicated a *syn* relationship of the C<sub>7</sub>-H with the C<sub>8</sub>-H. To have further insight, the diene **4b** was prepared from the ketone **1** on reaction with methallyl magnesium chloride followed by the sequence of reactions analogous to the synthesis of the diene **4a**. UV irradiation of this diene **4b** in diethyl ether solution in the presence of CuOTf catalyst provided the crystalline adduct **5b**, mp 58°C in 72% yield. The C<sub>7</sub>-H in debenzylated adduct **6b** displayed a coupling constant of 6.3 Hz again indicating a *syn* relation between the C<sub>7</sub> and C<sub>8</sub> hydrogens. Finally, the *cis-syn-cis* structure of the photo-

toadduct **5b** was unequivocally established by a single crystal X-ray structure.<sup>11</sup>

Exclusive formation of a thermodynamically less stable *cis-syn-cis* linearly arrayed tricyclic system in a cycloaddition reaction is noteworthy. The formation of *cis-syn-cis* adducts<sup>12</sup> in a [2+2] photocycloaddition has been observed only when the reacting alkenes are preorganised through tethers. AM1 calculations<sup>13</sup> (using MOPAC, version 1.10) indicates that the *cis-syn-cis* adduct **5a** (*E*=−4865.8857 kcal mol<sup>−1</sup>) is less stable than the corresponding *cis-anti-cis* adduct **7** (*E*=−4869.0894 kcal mol<sup>−1</sup>) by 3.2 kcal mol<sup>−1</sup> in the gas phase. Thus, one would expect the formation of the *cis-anti-cis* adduct **7** from photocycloaddition of the diene **4a**. A plausible explanation for the formation of the *cis-syn-cis* adducts is the formation of the tricoordinated Cu(I) complex **8** prior to cycloaddition. This complex preorganises the diene for cycloaddition to take place *syn* to the furanose ring leading to the formation of the *cis-syn-cis* adducts. The involvement of an analogous tricoordinated Cu(I) complex during photocycloaddition of 3-hydroxy-1,6-heptadienes has been invoked<sup>10</sup> to explain the predominant formation of *endo*-2-hydroxy bicyclo[3.2.0]heptanes.



**3a**, R = CH<sub>2</sub>  
**9**, R = O  
**10**, R = CH=COOEt

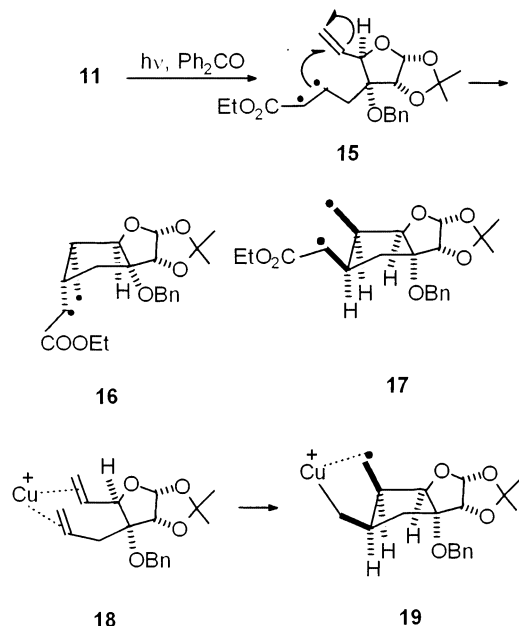


**12**, R<sup>1</sup> = Bn, R<sup>2</sup> = Et  
**13**, R<sup>1</sup> = H, R<sup>2</sup> = Et  
**14**, R<sup>1</sup> = R<sup>2</sup> = H

**Scheme 2. Reagents and conditions:** (i) OsO<sub>4</sub>, NaIO<sub>4</sub>, H<sub>2</sub>O, Et<sub>2</sub>O, 79%; (ii) NaH, (EtO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Et, THF, rt, 18 h, 67%; (iii) (a) 75% aq. AcOH, rt, 12 h, (b) I<sub>2</sub>, PPh<sub>3</sub>, imidazole, PhMe, reflux, 2 h, 54%; (iv) *hν*, Ph<sub>2</sub>CO, CH<sub>3</sub>CN, 6 h, 50%; (v) 10% Pd-C, H<sub>2</sub>, EtOH, AcOH, HClO<sub>4</sub>, 65%; (vi) KOH, H<sub>2</sub>O, EtOH, reflux, 2 h, 83%; (vii) *hν*, quinoline, *t*-BuSH, C<sub>6</sub>H<sub>6</sub>, 7 h, 40%.

To determine the stereochemical outcome in a [2+2] photocycloaddition in the absence of Cu(I) catalyst, the diene **10** having a conjugated ester moiety was chosen. The diene **10** was prepared as outlined in Scheme 2. Oxidative cleavage of the alkene unit in the benzyl derivative **3a** followed by Wittig–Horner reaction of the resulting aldehyde **9** afforded exclusively the *E*-isomer **10**. The ester **10** was then converted to the diene **11** by following a sequence similar to the transformation of the diacetone **3a** to the diene **4a**. The diene **11** could be made to undergo cycloaddition on irradiation of its acetonitrile solution in the presence of benzophenone as a sensitizer. A single photoadduct **12** was obtained as a liquid in 50% yield. The stereochemical assignment to the adduct **12** was based on its transformation to the cyclobutane derivative **6a** through debenzylation, hydrolysis and photodecarboxylation<sup>14</sup> of the resulting hydroxy acid **14**. Thus, sensitised photocycloaddition of the dienic ester **11** provided also a *cis-syn-cis* adduct **12**.

The observed stereochemical outcome in the photocycloaddition of the diene **10** may be explained by the well accepted pathway<sup>15</sup> as delineated in Scheme 3. Triplet sensitisation of the conjugated ester **11** leads to the biradical intermediate **15**. 5-*exo*-Trig addition of the high-energy β-radical to the double bond may give rise to two new biradical intermediates **16** and **17**. Preferential formation of the biradical **17** is expected over the



Scheme 3.

biradical **16** as the later experiences severe 1,3-diaxial interactions involving the benzyloxy group and the alkyl chains bearing the radicals. Such 1,3-diaxial interactions between alkoxy and alkyl groups have been found to determine the stereochemistry of the product in 5-*exo*-trig radical cyclisations.<sup>16</sup> Ring closure of the 1,4-biradical **17** then leads to the product **12**. In light of this observation, it is apparent that photocycloaddition of the diene **4** in the presence of Cu(I) catalyst does not proceed through the complex **8**. Instead, it probably proceeds through photoexcitation of the complex **18**. Sequential bond formation,<sup>17</sup> similar to the sensitised process, preferentially leads to the radical intermediate **19** which finally collapses to the product. Thus, the unusual stereochemical outcome in both the Cu(I)-catalysed and -sensitised photocycloadditions arises from the steric effects of the substituents in the sugar template.

In conclusion, we have demonstrated that thermodynamically less stable *cis-syn-cis* linearly arrayed tricyclic structures, which are not usually obtained in cycloaddition reactions, can be synthesised in [2+2] photocycloaddition reactions through the correct choice of substrate and reaction parameters.

### Acknowledgements

We are grateful to Dr. Dipankar Datta of the Department of Inorganic Chemistry for the AM1 calculations. Financial support from CSIR, New Delhi through Grant No. 01(1625)/EMR-II is gratefully acknowledged. SPB thanks CSIR for a fellowship.

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- All new compounds reported here were duly characterised on the basis of spectral (IR, <sup>1</sup>H and <sup>13</sup>C NMR) and C, H microanalytical data. Spectral data for selected compounds. Compound **5b**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.26 (3H, s, Me), 1.36 (3H, s, Me), 1.59 (3H, s, Me), 1.76–2.15 (6H, m), 2.46 (1H, m), 4.47–4.57 (4H, m, PhCH<sub>2</sub>, C<sub>4</sub>-H and C<sub>7</sub>-H), 5.99 (1H, d, *J*=3.9 Hz, C<sub>5</sub>-H), 7.24–7.4 (5H, m, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 13.1 (CH<sub>2</sub>), 26.9 (Me), 27.0 (Me), 27.8 (Me), 34.3 (CH<sub>2</sub>), 38.1 (C), 44.6 (CH<sub>2</sub>), 46.6 (CH), 67.0 (CH<sub>2</sub>), 80.6 (CH), 87.4 (CH), 97.4 (C), 106.5 (CH), 112.5 (C), 127.4 (CH), 127.9 (CH), 128.2 (CH), 128.4 (CH), 128.8 (CH), 138.3 (C). Compound **6b**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.28 (3H, s, Me), 1.36 (3H, s, Me), 1.54 (3H, s, Me), 1.79–2.1 (6H, m), 2.48 (1H, m), 4.15 (1H, d, *J*=6.3 Hz, C<sub>7</sub>-H), 4.27 (1H, d, *J*=3.6 Hz, C<sub>4</sub>-H), 5.89 (1H, d, *J*=3.6 Hz, C<sub>5</sub>-H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 13.3 (CH<sub>2</sub>), 26.7 (Me), 26.9 (Me), 28.0 (Me), 29.7 (C), 34.2 (CH<sub>2</sub>), 46.7 (CH), 48.8 (CH<sub>2</sub>), 81.3 (CH), 88.2 (CH), 92.0 (C), 105.8 (CH), 112.4 (C). Compound **12**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.25 (3H, t, *J*=7.2 Hz, Me), 1.39 (3H, s, Me), 1.61 (3H, s), 2.21–2.50 (3H, m), 2.77–2.95 (3H, m), 3.09–3.20 (1H, m), 4.13 (2H, q, *J*=7.2 Hz), 4.49 (1H, d, *J*=11 Hz, PhCH), 4.50 (1H, d, *J*=4.8 Hz, C<sub>7</sub>-H), 4.61 (1H, d, *J*=11 Hz, PhCH), 4.62 (1H, d, *J*=3.9 Hz, C<sub>4</sub>-H), 5.98 (1H, d, *J*=3.9 Hz, C<sub>5</sub>-H), 7.14–7.36 (5H, m); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 14.6 (Me), 21.0 (CH<sub>2</sub>), 27.2 (Me), 27.4 (Me), 38.6 (CH<sub>2</sub>), 38.7 (CH), 42.3 (CH), 45.3 (CH), 60.8 (CH<sub>2</sub>), 67.5 (CH<sub>2</sub>), 81.1 (CH), 86.0 (CH), 98.7 (C), 106.4 (CH), 113.1 (C), 127.8 (CH), 127.9 (CH), 128.7 (CH), 138.8 (C), 175.9 (CO).
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$D_c = 1.252 \text{ Mg m}^{-3}$ ,  $T = 100 \text{ K}$ ,  $\mu(\text{Mo K}\alpha) = 0.09 \text{ mm}^{-1}$ . A Smart-CCD diffractometer employing graphite-monochromated Mo K $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ) in the  $\omega = 2\theta$  scan mode was used to record 6298 reflections ( $R_{\text{int}} = 0.0313$ ). The structure was solved by direct methods (MULTAN-88) and refined by full-matrix least-squares (on  $F^2$ ) using SHELXL-93 with anisotropic thermal parameters to non-hydrogen atoms. The final residuals for 3555 reflections with  $|F_o| \geq 4\sigma|F_o|$  were  $R_1 = 0.0394$  and  $wR_2 = 0.0938$ . Crystallographic data for compound **5b** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 158331. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0) (1223)-336033; e-mail: deposit@ccdc.cam.ac.uk).

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